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13. ABSTRACT ***(Maximum 200 Words)***

Objectives were to verify the innovative concepts of non-invasive intracranial pressure (ICP) absolute value measurement and non-invasive cerebrovascular autoregulation (CA) continuous monitoring, to prove the design concepts and to perform the limited clinical trials of the new prototype devices. These devices were designed and successfully tested.
Slow intracranial and ABP wave correlation methodology was used for continuous CA invasive and non-invasive monitoring. Prototype of non-invasive CA monitor has been used together with invasive ICP and ABP slow wave monitors in the ICU. 13 patients with traumatic brain injuries were monitored and simultaneous 87 hour monitoring data were analyzed. Also a prototype of ultrasonographic absolute ICP meter was applied for non-invasive ICP measurements on 10 ICU patients following Clinical Research Protocol No.99124006, AIBS No.990135, HSSRB log No.A-9676. 57 simultaneous invasive and non-invasive absolute ICP measurements have been performed.
It has been shown experimentally under ICU conditions that non-invasive CA monitoring reflects the same CA dynamics as an invasive autoregulation monitoring. The hypothesis on the coincidence of invasive and non-invasive CA monitoring results was accepted. This conclusion is based on statistically significant clinical data of this research.
The results of non-invasive absolute ICP measurement method clinical assessment show that this is the only method for non-invasive ICP measurement without the problem of individual calibration of system "patient – non-invasive ICP meter". The hypothesis on zero value of differences between invasive and non-invasive absolute ICP measurements under comparison was accepted after analysis of statistically significant clinical data of this research.

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INTRODUCTION

The key objectives of the study were to verify the innovative concepts of non-invasive intracranial pressure (ICP) absolute value measurement and non-invasive cerebrovascular autoregulation (CA) continuous monitoring, to prove the design concepts and to perform the limited clinical trials of the new prototype devices. These devices were designed and successfully tested. The technological requirements for future development of deliverable prototype devices have been defined.

The first-year research accomplishment of this project was presented in our Annual Report (Project Title: Non-invasive Ultrasonic Diagnosing and Monitoring of Intracranial Pressure / Volume) covering the award performance period Oct 1, 2000 – Oct 1, 2001. Our previous Annual Report will be cited in this Final Report as "our Annual Report, 2001".

The key research accomplishment of the award performance period Oct 1, 2001 – Oct 1, 2002 was a clinical study of our non-invasive prototype devices on ICU patients with traumatic brain injuries.

Slow intracranial and ABP wave correlation methodology was used for continuous CA invasive and non-invasive monitoring. A prototype of non-invasive CA monitor has been used together with invasive ICP and ABP slow wave monitors in the ICU.

13 patients with traumatic brain injuries were monitored and 87 hours of simultaneous monitoring data were analyzed. Also a prototype of ultrasonographic non-invasive absolute ICP meter was used for non-invasive ICP measurements on 10 ICU patients following Clinical Research Protocol No.99124006, AIBS No.990135, HSSRB log No.A-9676.

57 simultaneous invasive and non-invasive absolute ICP measurements have been performed in ICU.

It has been shown experimentally under ICU conditions that non-invasive CA monitoring reflects the same CA dynamics as an invasive autoregulation monitoring. The hypothesis on the coincidence of invasive and non-invasive CA monitoring results was accepted after the statistical analysis of clinical data. This conclusion is based on statistically significant clinical data of this research.

The results of clinical assessment of a non-invasive absolute ICP measurement method show that this is the only method for non-invasive ICP measurement without the problem of individual calibration of the system "patient – non-invasive ICP meter". The hypothesis on zero value of differences between invasive and non-invasive absolute ICP measurements under comparison was accepted after the analysis of statistically significant clinical data of this research.

BODY

1.0. NON-INVASIVE ABSOLUTE ICP MEASUREMENT THROUGH THE HUMAN EYE

1.1. Background of non-invasive absolute ICP measurement

Neurological dysfunction resulting from brain injury is associated with a high mortality rate [1,2,3,4,6,7]. The economic burden of the injuries is also large [3]. Aspects of practical importance include an early detection of brain injury, an accurate quantification of the degree of the injury, and a reliable prediction of recovery outcome. Other diagnostic approaches are available to detect and assess brain injuries such as near infrared spectroscopy and cerebral blood velocity or flow using a laser Doppler flow meter or transcranial Doppler blood velocity meter. This project will investigate an innovative ultrasonic technology together with the method of ICP absolute value measurement through the human eye for the combat casualty care application.

Several experimental and clinical studies [4] verified the pathophysiological parameters such as cerebral blood flow (CBF) and ICP which can be employed to describe and assess the individual time course immediately following the brain injury. Non-invasive measurement of the ICP absolute value is extremely important for the early diagnosing of the brain injury in emergency cases before CT and MRI diagnosing, for military and aerospace medicine, for monitoring during transplantological procedures, etc [8-11]. It is expected that the non-invasive ICP technology developed here could provide a solution to some of the problems associated with the current invasive ICP monitoring. The problems include the increased risk of infection, limitations of invasive ICP monitoring duration, delays in obtaining ICP diagnosis in emergency due to the need of implanting the sensors.

1.2. Numerical simulation of absolute ICP value measurement technology (Vittamed)

The purpose of numerical simulation was to analyze the possible systematic error of the proposed non-invasive absolute ICP measurement method and to show that this method does not need the individual calibration of the system „individual patient – non-invasive ICP meter".

The mathematical model of blood flow in the eye artery is based on one-dimensional equations resulting from the Navier-Stokes equations (pulsatile incompressible flow in a flexible tube).

The blood flow in the eye artery mainly depends on the perfusion pressure, the artery diameter and hydrodynamic resistance in the eye microvessels.

The diameter of the eye artery depends on:
- elastic properties of the artery wall,
- elastic properties of the surrounding tissues,
- arterial blood pressure (ABP), ICP and external pressure Pe.

The mathematical model of numerical simulation of pulsating blood flow through the eye artery is based on the assumptions that the behaviour of eye artery and blood flow is axis-symmetric and that arterial pressure is constant across the artery. Therefore, blood flow can be modelled by one-dimensional equations resulting from the integration of three-dimensional non-compressible Navier-Stokes equations over the cross section of the artery. The artery is considered as an axis-symmetric elastic tube. As a result, time evolution of blood volume yield in the artery is described by a system of continuity and momentum equations as follows

$$\frac{\partial A}{\partial t} + \frac{\partial Q}{\partial z} = 0 \qquad (1)$$

$$\frac{\partial Q}{\partial t} = -\frac{A}{\rho}\frac{\partial p}{\partial z} - \frac{8\pi\mu}{\rho A}Q - \frac{\partial}{\partial z}\left(\frac{Q^2}{A}\right) \qquad (2)$$

where t is time, z is measured along the artery, $A(z,t)$ is the inner cross-section area of the artery, $Q(z,t)$ is the blood volume yield, $p(z,t)$ is an arterial blood pressure, μ and ρ are the blood viscosity and density, respectively.

The system is completed by the equilibrium equation of forces acting on the arterial wall:

$$p - p_{outer} = M\frac{\partial^2 r}{\partial t^2} + \gamma\frac{\partial r}{\partial t} + p_{elastic} + T\frac{\partial^2 r}{\partial z^2} \qquad (3)$$

where $r(z,t)$ is the inner radius of the artery, p_{outer} – pressure acting on the outer wall of the artery and is a function of z, M is related to the density of the the wall, $T(r,z)$ – longitudinal tensile force, γ is the damping coefficient for wall motion, $p_{elastic}$ is pressure created by the elastic force of the arterial wall and is defined as follows

$$p_{elastic} = p_0 \exp\left(k\frac{A - A_0}{A_0}\right) \qquad (4)$$

where r_0 is the artery inner radius, while arterial pressure is p_0 and $k(z)$ is arterial stiffness.

The simulation area is divided into three zones: itracranial (inside the brain), inside the cranial canal, and extracranial, what defines different outer pressure: p_{outer} is equal to ICP inside the brain and p_{outer} is equal to the external pressure applied to the eye in the extracranial segment of the eye artery. Under assumption that the eye artery does not pulsate inside the cranial canal, the inner radius of the artery inside the cranial canal is constant. As a result, the equilibrium equation (3) is not solved inside the cranial canal. All zones are coupled during calculations.

Boundary conditions are defined by inlet pressure p_{in}(t) or blood yield Q_{in}(t). As for example, an input yield Q_{in}(t) is approximated by the function displayed in Fig. 1, which is close by the shape to the arterial blood pressure pulse. Results of numerical simulation of absolute ICP value measurement are presented in Fig. 2 - Fig.4.

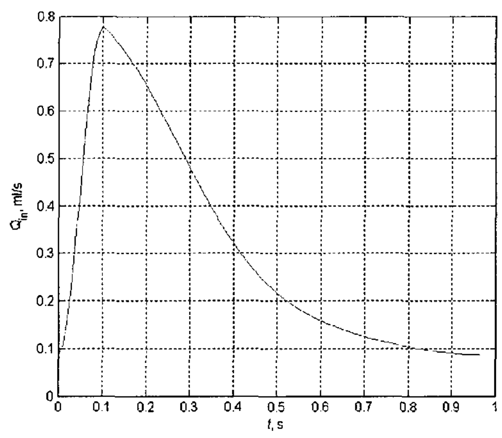


Fig. 1. Inlet blood volume yield of the eye artery

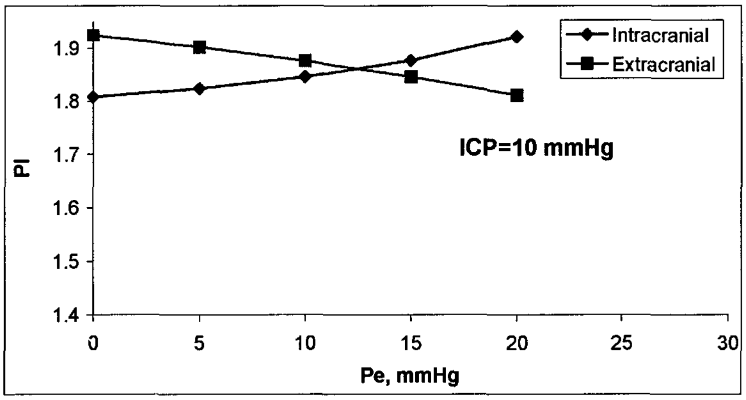


Fig. 2. Numerical simulation of the relationships between pulsatility indexes PI in the intracranial and extracranial segments of the eye artery on extracranial pressure Pe applied to the eye: when absolute ICP value was equal to 10 mmHg, the balance between intracranial and extracranial PI values was obtained at the point Pe=12.5 mmHg

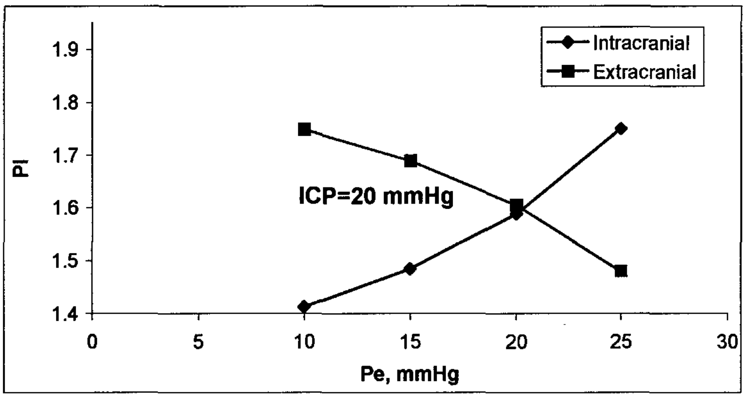
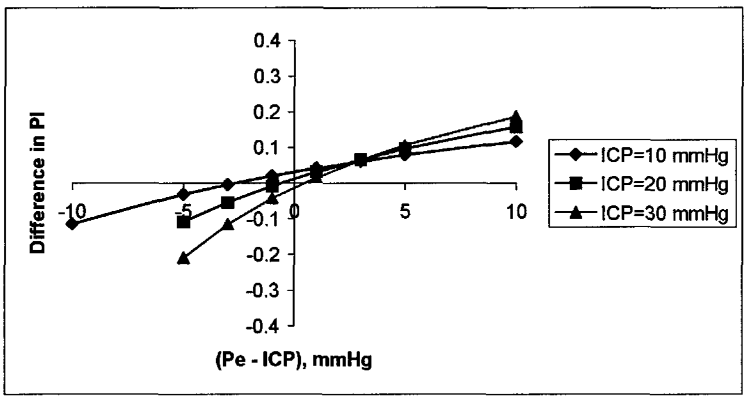
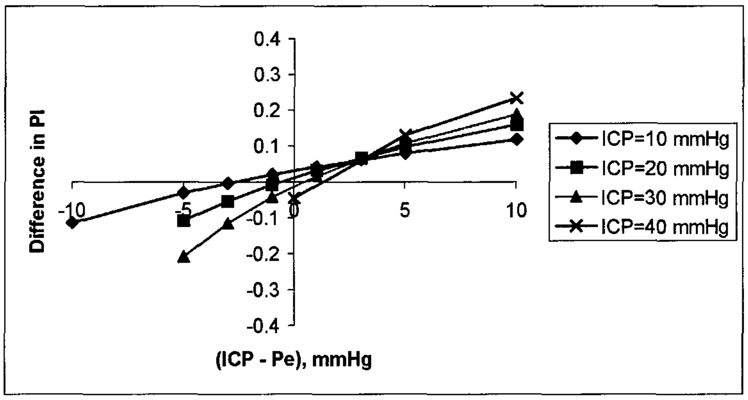


Fig. 3. Numerical simulation of the relationships between pulsatility indexes PI in the intracranial and extracranial segments of the eye artery on extracranial pressure Pe applied to the eye: when absolute ICP value was equal to 20 mmHg, the balance between intracranial and extracranial PI values was obtained at the point Pe=21 mmHg



a)



b)

Fig. 4. Relationships between the differences of intracranial PI and extracranial PI depending on Pe and ICP: a) numerical model with constant mean blood flow in the eye artery, b) numerical model with Pe dependent mean blood flow in the eye artery

It is shown on Fig. 4 a) and b) that the ICP dependent systematic error of the proposed non-invasive method is within limits from –3 mmHg to +1 mmHg when the absolute ICP values are from ICP=10 mmHg to ICP=40 mmHg. This absolute systematic error is small enough and it is not important in clinical practice.

Results of numerical simulation of non-invasive absolute ICP measurement show the possibility to measure absolute ICP value without the necessity to eliminate such a small systematic error of the proposed method. This result shows that this is only method which does not need the calibration of the system "individual patient – non-invasive ICP meter" because of clinically non-significant absolute ICP measurement errors in the ICP range from 0 mmHg up to 40 mmHg, i.e., below and above the critical ICP threshold 20 ... 25 mmHg.

1.3. Clinical study of non-invasive absolute ICP measurement device

1.3.1. Clinical research objectives

(Clinical Research Protocol No.99124006, AIBS No.990135, HSSRB log No.A-9676):

To conduct a clinical trial on intensive care unit coma patients with heads injuries and implanted existing standard invasive intracranial pressure (ICP) transducers connected to standard ICP monitors, applying simultaneously multidepth transcranial Doppler (TCD) measurements of the eye artery blood flow parameters in the intracranial and extracranial segments of that artery in the case of ICP equal to the external pressure applied to the eye.

1.3.2. Expected study population

(Clinical Research Protocol No.99124006, AIBS No.990135, HSSRB log No.A-9676):

- Male and female subjects >18 years of age with traumatic brain injury.

We intended to study 10 patients with traumatic brain injury. Inclusion criteria: age >=18 years, brain injured patients monitored in an intensive care unit who have invasive arterial and intracranial pressure monitoring. Indications for intracranial pressure monitoring are appropriate in patients with severe head injury with abnormal admission CT scan. Severe head injury is defined as a Glasgow Coma Scale Score of 3-8 after cardiopulmonary resuscitation. An abnormal CT scan of the head is one that reveals hematomas, contusions, edema, or compressed basal cisterns. ICP monitoring is appropriate in patients with severe head injury with a normal CT scan if two or more of the following features are noted at admission: age over 40 years,

unilateral or bilateral motor posturing, systolic blood pressure less than 90 mmHg. ICP monitoring is not routinely indicated in patients with mild or moderate head injury (Guidelines for the Management of Severe Head Injury. Brain Trauma Foundation, USA, 1995). Following the Guidelines for the Management of Severe Head Injury, only comatose patients of ICU with implanted invasive ICP monitoring transducers will be involved in the study.

- Post Sub-arachnoid haemorrhage patients monitored in an intensive care unit who have invasive arterial and intracranial pressure monitoring. Exclusion criteria: patients with wounds, scars or a craniotomy overlying the optimal window for transintracranial ultrasonic measurement.

1.3.3. Declaration of a specific number of subjects for sample size

The goal of the experimental tests is the evaluation of the reliability of data obtained using new non-invasive intracranial pressure measurement methods in comparison with the invasively measured data using an intracranial pressure monitor.

The proposed non-invasive intracranial pressure measurement method does not influence the physiological state of the patient. From the methodological point of view the object of investigation is not the individual patient but the physical parameter (intracranial pressure measured by two ways - invasively and non-invasively), reflecting the dynamics of the physiological state of an individual patient. Therefore, a separate patient can be repeatedly exploited to obtain the required statistics of sample data. The parameter values during measurement tests must cover the entire range of the parameter variation under various physiological states of patients.

The sample data is obtained during a separate measurement cycle of 1 hour duration at which the parallel measurement data from the investigated measurement device and the standard measurement device are registered. In this way, up to 180 000 parallel measurement points are obtained at each measurement cycle. For the data obtained, the Student's distribution statistics test for paired or correlated samples [13] with the significance level 5% is applied to evaluate a coincidence of the measurement results. Therefore, for each measurement cycle a decision is stated (to accept or reject the hypothesis on the coincidence of results).

The consistency of the decisions is to be tested for repeated measurement cycles under various physiological states of patients. The number of measurement cycles is calculated using a general formula for the significance test of a single proportion [14]:

$$n > \frac{\left[u\sqrt{\pi(1-\pi)} + v\sqrt{\pi_0(1-\pi_0)}\right]^2}{(\pi - \pi_0)^2}, \qquad (1)$$

where

n - required minimum size of measurement cycles;

π - proportion of interest;

π_0 - null hypothesis proportion;

u - one-sided percentage point of the normal distribution corresponding to 100% - *power*;

v - percentage of the normal distribution corresponding to the required (two-sided) significance level.

For our investigation we have introduced the following values of the formula (1) parameters:

For our investigation we have introduced the following values of the formula (1) parameters: the proportion of interest $\pi = 0.95$; the null hypothesis (measurement results by the investigated and standard methods coincide) proportion $\pi_0 = 1$; the power value for demonstrating the significant difference between results of measurement cycles is accepted $power = 95\%$, which corresponds $u = 1.645$; the significance level is accepted 5%, which corresponds $v = 1.96$.

With the above parameter values, the following value of the required measurement cycles is calculated:

$$n > \frac{\left[1.645\sqrt{0.95(1-0.95)} + 1.96\sqrt{1(1-1)}\right]^2}{(0.95-1)^2} = 52 \qquad (2)$$

Under specific experimental conditions, a separate patient can be tested 2 times per day during 5 days. Therefore, the maximum 10 measurement cycles can be obtained from one patient, and the minimum number of patients to obtain the required statistics of samples is

$$whole\ number\left(\frac{52}{10}\right) = 6 \text{ (patients).} \qquad (3)$$

The real number of measurement cycles obtained from one patient, however, can be less than 10 (in practice it varies from 1 to 10), if the physiological state of the patient does not change and the repeated measurement cycles are not informative. The criteria of change are: the state of blood flow autoregulation is changed, or CPP, ABP or ICP values are significantly changed, or B waves became active.

Taking into account the above circumstances, we have increased the calculated value to 10 patients in order to ensure the required statistics of samples under unfavourable experimental conditions.

1.3.4. Specification of the statistical power analysis

As it has been demonstrated by the calculation presented above, the statistics of informative number of measurement cycles $N > 52$ provides the required power of conclusions. The number of subjects to obtain the required statistics of samples is determined to be 10.

Assuming an idealistic case, if the maximum number of informative samples (10) is obtained from each patient, the whole number of samples available for statistical analysis is $10 \times 10 = 100$. This number significantly exceeds the required minimum value ($N > 52$). Thus, experimental data available from 10 patients provide a significant reserve for obtaining the required statistics of informative samples, taking into account that the real number of informative samples obtained from a separate patient can be less then 10.

A more exact statistical calculation of the required number of subjects can not be performed, as there is no *a priori* information about statistical distribution of the numbers of informative samples obtained from one patient.

Referring to the above reasoning, we have determined the number 10 of subjects as a

definitive number for obtaining the required statistics of samples.

Under extremely unfavorable conditions of experimental tests, if the minimum number ($N > 52$) of informative samples were not obtained from 10 patients, the experimental research will be extended by introducing extra patients until the required number of informative samples is obtained.

1.3.5. The clinical data analysis plan

1. *Processing the measurement cycles of experimental data in order to evaluate for each measurement cycle a coincidence of measurement data from the investigated measurement device and the standard measurement device.*

Calculation is based on the paired data of parallel measurements

$$\left(x_{inv}\right)_i, \left(x_{st}\right)_i, \ i = 1, \ \ldots, \ n, \tag{4}$$

where $\left(x_{inv}\right)_i$ is the measured value by the investigated device; $\left(x_{st}\right)_i$ is the measured value by the standard device; i is the index of measurement point; and n is the number of measurement points (up to $180\ 000$).
For each measurement point a difference is calculated:

$$D_i = \left(x_{inv}\right)_i - \left(x_{st}\right)_i, \quad i = 1, \ \ldots, \ n. \tag{5}$$

Testing the hypothesis on the equality of the population means is based on the calculated value of the t-test statistics [12]:

$$T = \frac{m_D - 0}{\frac{s}{\sqrt{n}}}, \tag{6}$$

which is distributed as Student's t with $n-1$ degrees of freedom.

Parameters m_D (mean) and s (standard deviation) are calculated using formulas:

$$m_D = \frac{1}{n}\sum_{i=1}^{n} D_i, \tag{7}$$

$$s = \sqrt{\frac{1}{n-1}\sum_{i=1}^{n}\left(D_i - m_D\right)^2}. \tag{8}$$

The calculated value T is compared with the critical value t, obtained from the statistical table of t-distribution values for the $n-1$ degrees of freedom and 5% significance level.

If $|T| < t$, the hypothesis on the equality of the population means is accepted, otherwise the hypothesis is rejected.

In this way, for each measurement cycle a decision is stated: accept or reject the hypothesis on the coincidence of results.

2. *Statistical analysis of the results of the informative measurement cycle tests in order to evaluate a coincidence of measurement results for the entire population of samples.*

For the investigated number N of informative samples ($N > 52$), a proportion π_{N+} of samples (N_+) with the positive decision on the coincidence of measurement results is calculated:

$$\pi_{N+} = N_+ / N. \tag{9}$$

The calculated value π_{n+} is compared with the proportion of interest $\pi = 0.95$.

If $\pi_{N+} > \pi$, the hypothesis on the coincidence of measurement results is accepted. Otherwise the hypothesis is rejected.

1.3.6. Clinical data of simultaneous invasive and non-invasive absolute ICP measurements

A clinical study of absolute ICP value measurement technique (two-depth TCD technology) has been performed in order to evaluate a coincidence of invasive and non-invasive empirical results.

ICP absolute value measurement through the human eye is based on the simultaneous ultrasonic measurement of the blood flow parameters in the intracranial and the extracranial segments of the eye artery (see our Annual Report from Sept 2001, pp. 21-24).

We found experimentally that the eye artery behaves passively to an applied transmural pressure. Blood flow velocity pulsations depend on ICP in the intracranial segment and depend on extracranial pressure (Pe) in the extracranial segment.

We also found experimentally that in the case of balance between ICP and Pe, when ICP = Pe, the same blood flow parameters – diastolic, systolic and mean values, pulsatility and resistivity indexes, etc., are approximately equal in the intracranial and extracranial segments of the eye artery. This balance does not depend on the individual anatomy of eye arteries or the eye arterial pressure and the hydrodynamic resistance of the eye artery hydrodynamic load.

The state of balance when ICP = Pe can be achieved by applying external pressure to the eye ball and surrounding tissues by means of a pneumatic camera. The state of balance is identified by measuring the blood velocity parameters of the eye artery through the application of the transcranial Doppler (TCD) multi-depth technique.

We performed a clinical study of our non-invasive absolute ICP measurement technique on 10 ICU patients with traumatic brain injuries (USAMRAA Award No: DAMD17-00-2-0065, Clinical Research Protocol No. 99124006). Invasive and non-invasive absolute ICP measurements were performed simultaneously in different pathophysiological states of the ventilated patients in coma below and above the critical level of ICP = 20...25 mmHg. Here Pe is an external pressure applied to the tissues surrounding the eyeball. The study population is presented in Table 1.

We applied a specially designed two-depth TCD device with a special ultrasonic transducer and the pressure chamber for application of extracranial pressure Pe to the tissues surrounding the eyeball for non-invasive absolute ICP measurements. Codman device "ICP Express" was used for simultaneous invasive absolute ICP measurements (see our Annual Report from Sept 2001,

pp. 18-21).

Table 1. Non-invasive absolute ICP measurement study: ICU patient population

Total	10
Gender: male	10
Age: Mean / Range	27.6/(18-70) years
Pathology: Closed severe traumatic brain injury	100 %
Simultaneous invasive and non-invasive absolute ICP measurement in ICU	57 sessions

Some typical dependences of averaged pulsatility indexes PI of the eye artery blood flow in the intracranial and extracranial segments on extracranial pressure Pe are shown in Fig. 5-8. The results of simultaneous ICP measurements are presented in Fig. 9, Fig. 10 and Table 2. The results of all 57 simultaneous invasive and non-invasive measurements on 10 ICU patients are presented in Appendix A.

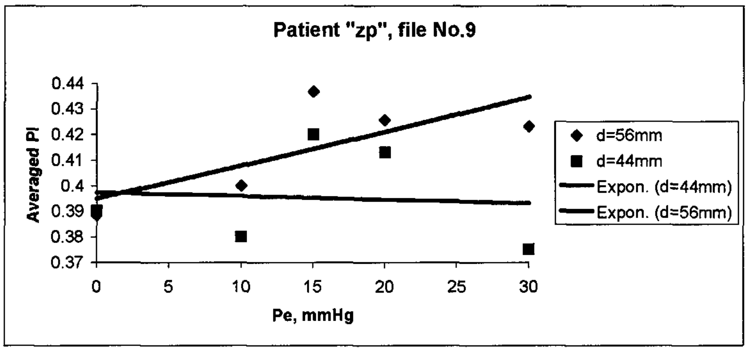


Fig. 5. Non-invasive measurement of absolute ICP value: invasive ICP=5 mmHg, non-invasive ICP=3 mmHg. d – depth from the surface of the eye lid: d = 44 mm for the extracranial segment and d = 56 mm for the intracranial segment of the eye artery

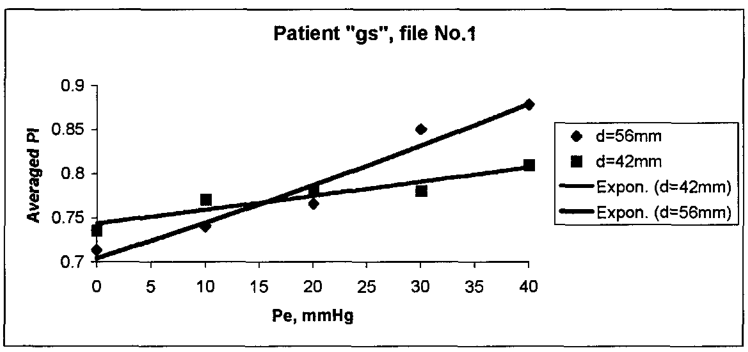


Fig. 6. Non-invasive measurement of absolute ICP value: invasive ICP=14 mmHg, non-invasive ICP=16 mmHg. d – depth from the surface of the eye lid: d = 42 mm for the extracranial segment and d = 56 mm for the intracranial segment of the eye artery

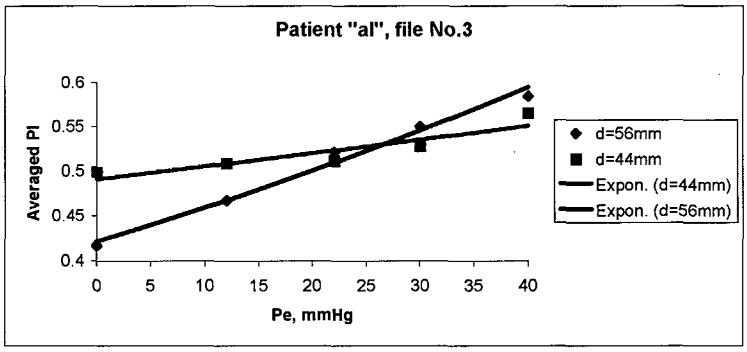


Fig. 7. Non-invasive measurement of absolute ICP value: invasive ICP=24 mmHg, non-invasive ICP=26 mmHg. d – depth from the surface of the eye lid: d = 44 mm for the extracranial segment and d = 56 mm for the intracranial segment of the eye artery

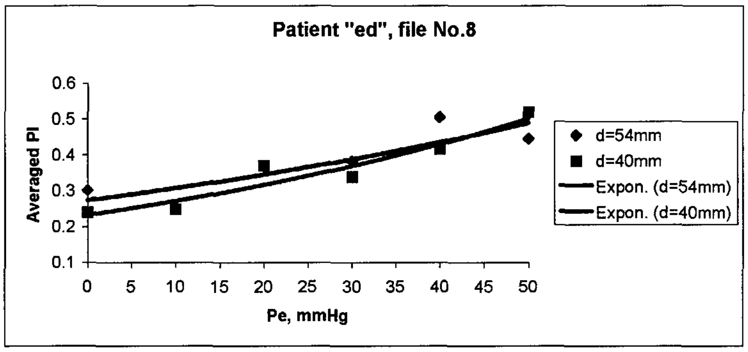


Fig. 8. Non-invasive measurement of absolute ICP value: invasive ICP=24 mmHg, non-invasive ICP=26 mmHg. d – depth from the surface of the eye lid: d = 40 mm for the extracranial segment and d = 54 mm for the intracranial segment of the eye artery

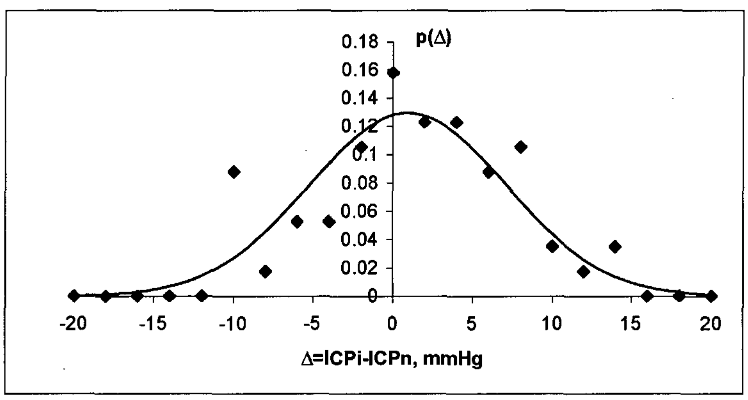


Fig. 9. Distribution p(Δ) of the difference between simultaneous invasive and non-invasive ICP measurements: mean μ=0.939 mmHg, standard deviation SD=6.18 mmHg

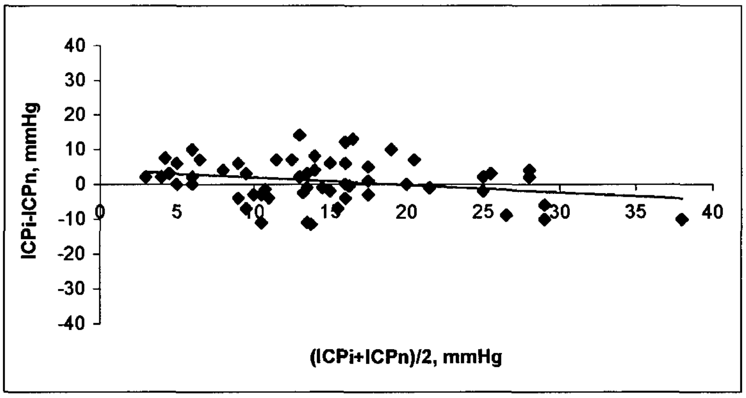


Fig. 10. Bland Altman plot of simultaneous invasive and non-invasive ICP measurements (10 patients with severe traumatic brain injuries, 57 simultaneous invasive and non-invasive measurements): red line – systematic error trend

Table 2. Invasive and non-invasive ICP measurements data

Patient No. and ID	Session No.	Invasive ICP, mmHg	Non-invasive ICP, mmHg
No.1, "sl"	1	8.5	11.5
	2	16	16
	3	14	18
	4	6	6
No.2, "dj"	5	8	19
	6	12	14.5
	7	14	12
	8	16	16.5
	9	10	6
	10	5	16
No.3 "rm"	11	8	19.5
	12	10	11.5
	13	6	13
	14	4	2
No.4, "gl"	15	6	3
No.5, "od"	16	24	34
	17	20	6
	18	18	17
	19	16	9
	20	14	15
No. 6, "ri"	21	11	8
	22	13	14
	23	15	8
	24	8	2
	25	12	19
	26	7	5
	27	9	13
No. 7, "zp"	28	15	12
	29	10	3
	30	12	6
	31	5	5
	32	8	0.5
	33	11	1
	34	7	11
	35	9	12
	36	5	3
	37	24	14
	38	26	32
	39	29	27
No. 8, "gs"	40	14	16
	41	16	19
	42	18	12
	43	22	31
No. 9, "ed"	44	24	17
	45	20	15
	46	23	10
	47	27	24
	48	30	26
	49	26	24
	50	21	22
	51	33	43
No. 10, "al"	52	18	10
	53	20	20
	54	24	26
	55	22	10
	56	19	13
	57	16	12

We were able to prove clinically for the first time that our non-invasive absolute ICP meter (Vittamed) is a non-invasive ICP meter which does not need an individual calibration of the system "individual patient – non-invasive ICP meter" because of clinically not significant systematic error of non-invasive measurements μ=0.939 mmHg (Fig. 10).

It is necessary to underline that clinically non-significant systematic error of absolute ICP measurement is achieved without calibration of our non-invasive ICP meter as it was predicted by mathematical modeling and our preliminary experiments.

The other attempts [14] to create the methods for ICP non-invasive measurements are based on some relationships between physical properties of some craniospinal or intracraniospinal biophysical objects (diameter of skull, resonance frequency of skull, thickness of dura mater, thickness of subarachnoid layer, resonance frequency of the pulsation of cerebral ventricles, tissue resonance frequency, pulsatility index of blood flow in cerebral arteries, etc., etc.) and absolute ICP. These relationships depend on a lot of influential factors including arterial blood pressure, cerebrovascular autoregulation state, the pathophysiological state of patients, etc. Such relationships are time-variable and need to be identified periodically. The only way of identification is to apply the periodical calibration of the system "individual patient – non-invasive ICP meter". In order to calibrate such a system it is necessary to apply a non-existing non-invasive absolute ICP meter with better accuracy than a non-invasive ICP meter under calibration. This situation is a paradox because such an accurate non-invasive absolute ICP calibrator still does not exist. Because of that the only solution of the problem is to measure absolute ICP non-invasively by applying the "Vittamed" non-invasive meter which is the only meter without the problem of calibration of the system "individual patient – non-invasive ICP meter".

The results of our clinical study (USAMRAA Award No: DAMD17-00-2-0065 (years 2001-2002), Clinical Research Protocol No. 99124006) support our hypotheses that the balance between ICP and extracranial pressure Pe applied to the eye can be achieved and identified applying multi-depth TCD technology with clinically non-significant systematic errors of absolute ICP measurement.

1.4. STATISTICAL TESTING OF THE HYPOTHESIS ON ZERO VALUE OF DIFFERENCES BETWEEN INVASIVE AND NON-INVASIVE ICP MEASUREMENTS

1.4.1. Testing the hypothesis

Testing the hypothesis on zero value of differences between the invasive and non-invasive ICP measurements (Table 2) is based on calculated value of the Student's t -test statistics:

$$T = \frac{m_D - 0}{\frac{s}{\sqrt{n}}}, \tag{5}$$

which is distributed as Student's t with $n-1$ degrees of freedom.

Parameters m_D (mean) and s (standard deviation) are calculated using formulas:

$$m_D = \frac{1}{n}\sum_{i=1}^{n} D_i, \tag{6}$$

$$s = \sqrt{\frac{1}{n-1}\sum_{i=1}^{n}\left(D_i - m_D\right)^2}, \tag{7}$$

where D_i are measured values of differences.

The calculated value T is compared with the critical value t, obtained from the table of t - distribution values for the $n-1$ degrees of freedom and significance level of the test (size of the

critical region) α. If $|T| < t_{n-1,\ 1-\alpha/2}$, the hypothesis on the equality of the population means is accepted, otherwise the hypothesis is rejected.

By processing the data presented in Table 2 we obtain:
$n = 57$, $m_D = 0.9386$ mmHg, $s = 6.1775$ mmHg and $T = 1.1471$.
The critical value of t-statistics for $\alpha = 5\%$ and $n = 57$ is $t_{n-1,\ 1-\alpha/2} \approx 2.00$.

$$|T| = 1.1471 < t_{n-1,\ 1-\alpha/2} = 2.00. \tag{8}$$

Therefore, the hypothesis on zero value of differences between invasive and non-invasive absolute ICP measurements under comparison is accepted.

1.4.2. Conclusion of clinical study

It is proved clinically for the first time that the non-invasive absolute ICP meter "Vittamed" is the only non-invasive ICP meter which does not need individual calibration of the system "patient – non-invasive ICP meter". The hypothesis on zero value of differences between invasive and non-invasive measurements has been proved by t-test statistics $|T|=1.1471<2.0$ (57 invasive / non-invasive measurements, ICP range from 4 mmHg to 33 mmHg, 10 patients, $\mu=0.939$ mmHg).

1.5. TECHNOLOGICAL REQUIREMENTS FOR NON-INVASIVE ABSOLUTE ICP METER PROTOTYPE DEVELOPMENT

The requirements for the development and design of the new more advanced deliverable prototype device for non-invasive absolute ICP measurement through the human eye are as follows:

1. To create an advanced software solution for on-line indication of spatial positioning and adjustment mode of ultrasonic transducer in order to obtain Doppler signals with the best signal to noise ratio from the two segments of the eye artery – intracranial segment and extracranial segment simultaneously.

2. To create an advanced software solution for identification and interactive or automatic elimination of Doppler signal artifacts on-line and simultaneously in intracranial and extracranial segment of the eye artery.

3. To create an advanced software solution for Doppler frequency shift signal optimized filtering on-line. The non-standard pulsatility indexes should be calculated in real time and compared in the intracranial and extracranial segments of the eye artery after the optimized filtering procedures.

4. To create an advanced software solution for the automatic adjustment of the optimized filter by the patient's heart rate changes during TCD measurements.

5. To create advanced hardware and software solutions in order to identify the informative TCD signals superposed with disturbing echoes from various not moving anatomical reflectors and to select only the informative TCD signal in order to insure the proper accuracy of the ultrasonic signal processing in its receiver.

6. To improve the hardware solutions for the received ultrasound signal processing for better signal-to-noise ratio (at least two times better), better resolution (at least 3 – 4 times) for low

diastolic blood flow velocity values (less than 10 cm/s).

7. To create software solutions for the on-line indication of the point of balance between the intracranial pressure and pressure applied to the eye in order to indicate the non-invasively measured absolute ICP value at the point of balance.

8. To create the data transfer protocol and software solutions for the connection of the "black box"-type special two-depth TCD hardware to the notebook PC.

2.0. NON-INVASIVE ICP / VOLUME REAL-TIME MONITORING ASSESSMENT IN ICU

2.1. Background

A wide variation in autoregulatory status in patients with severe head injury makes the treatment based on targeting ICP or CPP far from optimal. According to this reasoning, when patients have a predominantly diffuse brain injury and exhibit the phenomenon of impaired cerebrovascular autoregulation (CA) the Lund (Sweden) approach may be an important option of patient treatment. The Lund approach is totally opposite to the targeting CPP approach. The Lund approach is based on the use of permissive low CPP if brain oxygen supply is sufficient. The application of different treatment strategies and fine-tuning the management of increased ICP can only be rationally applied if therapeutic decisions are based on the accurate knowledge of the autoregulatory status of the patient brain blood flow. In order to decide which approach of traumatic brain injury treatment for one or other autoregulatory state of one or another patient is suitable, it is necessary to use continuous cerebrovascular autoregulation state monitoring [15-29].

"Vittamed" time-of-flight non-invasive ICP / volume real-time slow wave monitoring technology (see our Annual Report Sept 2001, pp. 33-45) was clinically assessed at the first time during this clinical research study. The same technology was modified and used for simultaneous invasive and non-invasive cerebrovascular autoregulation continuous monitoring study in ICU.

2.2. Clinical study of non-invasive continuous slow intracranial blood volume waves monitoring and cerebrovascular autoregulation state monitoring

2.2.1. Clinical research objectives

(Clinical Research Protocol No.99124006, AIBS No.990135, HSSRB log No.A-9676):

To conduct a clinical trial on intensive care unit coma patients with head injuries and implanted existing standard invasive intracranial pressure (ICP) transducers connected to standard ICP monitors simultaneously with a new noninvasive ICP/volume monitor above the critical level ICP = 20...25 mmHg and below this level. To investigate the ability to apply a new noninvasive ICP/volume monitor for continuous monitoring of a head injured patient's cerebral blood flow autoregulation state.

2.2.2. Expected study population

(Clinical Research Protocol No.99124006, AIBS No.990135, HSSRB log No.A-9676):

Male and female subjects >18 years of age with traumatic brain injury.

We intended to study 10 patients with traumatic brain injury. Inclusion criteria: age >=18 years, brain injured patients monitored in an intensive care unit who have invasive arterial and intracranial pressure monitoring. Indications for intracranial pressure monitoring are appropriate in patients with severe head injury with abnormal admission CT scan. Severe head injury is defined as a Glasgow Coma Scale Score of 3-8 after cardiopulmonary resuscitation. An abnormal CT scan of the head is one that reveals hematomas, contusions, edema, or compressed basal cisterns. ICP monitoring is appropriate in patients with severe head injury with a normal CT scan if two or more of the following features are noted at admission: age over 40 years, unilateral or bilateral motor posturing, systolic blood pressure less than 90 mmHg. ICP monitoring is not routinely indicated in patients with mild or moderate head injury (Guidelines for the Management of Severe Head Injury. Brain Trauma Foundation, USA, 1995). Following

the Guidelines for the Management of Severe Head Injury, only comatose patients of ICU with implanted invasive ICP monitoring transducers will be involved in the study.

Post Sub-arachnoid haemorrhage patients monitored in an intensive care unit who have invasive arterial and intracranial pressure monitoring. Exclusion criteria: patients with wounds, scars or a craniotomy overlying the optimal window for transintracranial ultrasonic measurement.

2.2.3. Clinical data of non-invasive continuous slow intracranial blood volume waves monitoring and cerebrovascular autoregulation state monitoring

Clinical data have been obtained following Clinical Research Protocol No.99124006, AIBS No.990135, HSSRB log No.A-9676. Invasive ICP monitors Camino V420 and Codman ICP Express have been used simultaneously with the non-invasive "Vittamed" monitor in the ICU on coma patients. Study population is shown in Table 3.

Table 3. ICU patient population

Total	13
Gender: male/female	10 (76.9%) / 3(23.1%)
Age: Mean / Range	30.5/(18-64) years
Pathology: Closed severe traumatic brain injury	100 %
Mean ABP range, mmHg	35 – 140
Mean ICP range, mmHg	3 – 80
Cerebrovascular autoregulation simultaneous invasive and non-invasive monitoring	53 one hour sessions
Slow intracranial B waves simultaneous invasive and non-invasive monitoring	87 one hour sessions

Experimental data are shown in Appendix B and Appendix C.

2.2.4. Statistical evaluation of the clinical data

The two type data sets have been used for statistical evaluation. The first type data sets contain all measurement points of sampling period (Table 4). The second type data sets contain randomly selected data points (Table 5).

Table 4. Experimental data processing results

Patient	Code of paired data set	Number of measurement points	Calculation of test statistics			Correlation coefficient
			Mean of differences	Standard deviation	Value of t-criterion	
1	2	3	4	5	6	7
AB	ab2&ab3	703	-0.0047	0.4015	**-0.3078**	**0.9194**
	ab4&5&6	703	-0.0046	0.5809	**-0.2087**	**0.8313**
	ab6_part2&ab8	703	-0.0039	0.6629	**-0.1542**	**0.7803**
AG	ag4_19part2	703	0.0045	0.9186	**0.1304**	**0.5780**
	ag4_19part3	503	-0.0040	0.8418	**-0.1075**	**0.6457**

AS	as1&as4_1	703	0.0030	0.8509	**0.0937**	**0.6380**
	as2&as9	703	0.0099	0.8294	**-0.3175**	**0.6560**
	as3	703	-0.0026	0.6363	**-0.1097**	**0.7976**
	as4_2	700	0.0024	0.8065	**0.0775**	**0.6748**
	as7_1	703	-0.0046	0.9805	**-0.1248**	**0.5193**
	as7_2	703	0.0022	1.0443	**0.0557**	**0.4548**
	as8_1	703	0.0033	0.6960	**0.1246**	**0.7578**
	as8_2	700	-0.0056	0.7358	**-0.2022**	**0.7294**
	as10	701	0.0055	0.9273	**0.1565**	**0.5701**
	as12	703	-0.0022	1.0564	**-0.0541**	**0.4421**
DJ	dj8	703	-0.0025	0.5090	**-0.1285**	**0.8704**
	dj13_15	703	0.0021	0.5320	**0.1062**	**0.8585**
	dj23_24	703	-0.0063	0.6321	**-0.2641**	**0.8002**
	dj28_32&dj44part1	703	-0.0036	0.3647	**-0.2640**	**0.9335**
	dj44part2&dj47_52	698	0.0017	0.6359	**0.0709**	**0.7978**
	dj57&dj59	703	0.0011	0.3806	**0.0788**	**0.9276**
	dj76-80	703	0.0178	0.9698	**0.4863**	**0.5298**
KV	kv1	703	-0.0019	0.7247	**-0.0687**	**0.7374**
	kv2_6part1	703	0.0056	0.7290	**0.2040**	**0.7343**
	kv2_6part2	687	-0.0036	0.4977	**-0.1894**	**0.8761**
MM	mm3_13part1	703	-0.0025	0.7086	**-0.0934**	**0.7489**
	mm55&mm59_1	703	0.0088	0.8156	**0.2858**	**0.6674**
	mm57_1	703	-0.0015	0.9267	**-0.0418**	**0.5706**
	mm57_2	703	0.00047	0.8543	**0.0146**	**0.6351**
	mm57_3	703	-0.0020	0.7913	**-0.0666**	**0.6869**
	mm57_5	703	0.000226	0.8923	**0.0067**	**0.6019**
	mm59_2	703	-0.0044	0.7632	**-0.1519**	**0.7088**
	mm60_1	703	0.0022	0.7264	**0.0818**	**0.7361**
	mm60_2	701	-0.0016	0.7339	**-0.0591**	**0.7307**
	mm3_13part2&mm15_22	623	-0.0079	0.6977	**-0.2816**	**0.7566**
RM	rm_1v	703	0.0025	0.5109	**0.1306**	**0.8695**
	rm_2v	703	-0.0094	0.4497	**-0.5542**	**0.8989**
	rm_3v	703	-0.0069	0.3637	**-0.5025**	**0.9339**
	rm_4v	504	-0.0064	0.2785	**0.5190**	**0.9612**
	rm_g4g5g6	703	-0.0124	0.4743	**-0.6925**	**0.8875**
	rm-v100	703	-0.0010	0.2058	**-0.1313**	**0.9788**
	rm-101&v105&v106	703	-0.0100	0.4377	**-0.6060**	**0.9042**
	rm-v107&v119&v14	689	0.000186	0.4533	**0.0108**	**0.8972**
SL	sl2-3	703	0.0015	0.5032	**0.0776**	**0.8734**
	sl7	693	-0.0029	0.5068	**0.1482**	**0.8716**
	sl21_26part1	703	0.0018	0.2566	**-0.1853**	**0.9671**
	sl21_26part2	591	-0.0140	0.5508	**-0.6198**	**0.8483**
	sl28-33part1	703	-0.0027	0.5471	**-0.1319**	**0.8503**
	sl28-33part2	697	0.0043	0.8394	**0.1341**	**0.6477**
	sl41&48	703	-0.0029	0.7319	**-0.1044**	**0.7322**
VD	vd11_26part1	703	0.0013	0.4169	**0.0802**	**0.9131**
	vd11_26part2	703	0.0032	0.4472	**0.1894**	**0.9000**
	vd11_26part3	703	-0.0016	0.3193	**-0.1339**	**0.9490**
	vd27_44part1	504	0.0024	0.3841	**0.1685**	**0.9262**
	vd27_44part2	703	0.0017	0.5306	**0.0835**	**0.8592**
	vd27_44part3	469	-0.0060	0.4384	**-0.2974**	**0.9039**
VG	vg4	703	-0.00028	0.8469	**-0.0089**	**0.6413**
	vg7&vg10part1	703	0.0062	0.4796	**0.3408**	**0.8850**
	vg10part2&vg2	703	-0.00015	0.4871	**-0.0081**	**0.8814**
	vg12	703	-0.000093	0.3784	**-0.0065**	**0.9284**
	vg15&18	703	-0.0203	0.8824	**-0.6114**	**0.6107**
	vg21part1	703	0.0076	0.9253	**0.2173**	**0.5719**
	vg21part2	703	0.0060	0.9580	**0.1651**	**0.5411**

VYB	vyb1_3	703	0.0013	0.6129	**0.0542**	**0.8122**
	vyb6	684	0.0021	0.2924	**0.1834**	**0.9573**
	vyb7	682	-0.0014	0.3049	**-0.1235**	**0.9535**
	vyb8	702	0.000935	0.2583	**0.0959**	**0.9666**
	vyb9_13	696	0.0066	0.5187	**0.3334**	**0.8655**
	vyb14&16	703	0.0073	0.6780	**0.2837**	**0.7701**
	vyb17_21	703	0.0015	0.2752	**0.1461**	**0.9621**
VM	vk1_3	703	-0.0056	0.6114	**-0.2447**	**0.8131**
	vm4&vm21_23	637	-0.000445	0.8477	**-0.0132**	**0.6407**
	vm5_10	703	0.0051	0.8433	**0.1613**	**0.6445**
	vm11	703	-0.0011	0.9820	**-0.0293**	**0.5178**
	vm12	692	0.0026	0.8511	**0.0797**	**0.6378**
	vm14_17part1	703	0.0043	0.5582	**0.22204**	**0.8442**
	vm14_17part2	703	0.0053	0.5340	**0.2645**	**0.8574**
	vm14_17part3	703	0.0051	0.5608	**0.2390**	**0.8428**
	vm14_17part4	703	0.0040	0.5773	**0.1826**	**0.8334**
	vm14_17part5	703	0.0014	0.6510	**0.0574**	**0.7881**
	vm20	703	-0.0038	0.5545	**-0.1822**	**0.8462**
JR	jr1-4_part1	703	0.0012	0.4783	**0.0683**	**0.8856**
	jr1-4_part2	703	-0.0019	0.4242	**-0.1214**	**0.9100**
	jr1-4_part3	635	0.0135	0.7042	**0.4843**	**0.7521**
	jr5-6	639	0.0027	0.5705	**0.1175**	**0.8373**
	jr7part1	703	0.0074	0.8344	**0.2358**	**0.6519**
	jr8	703	0.0053	0.8283	**0.1708**	**0.6569**

Table 5. Experimental data processing results

Patient	Code of paired data set	Number of measurement points	Calculation of test statistics			Correlation coefficient
			Mean of differences	Standard deviation	Value of t-criterion	
1	2	3	4	5	6	7
AB	ab2&ab3	70	-0.0965	0.3845	**-2.0998**	**0.9314**
	ab4&5&6	70	-0.0280	0.6204	**-0.3779**	**0.7899**
	ab6_part2&ab8	70	-0.0809	0.6553	**-1.0325**	**0.7739**
AG	ag4_19part2	70	-0.0539	0.8261	**-0.5458**	**0.6465**
	ag4_19part3	50	-0.0683	0.9008	**-0.5365**	**0.5800**
AS	as1&as4_1	70	0.1181	0.7123	**1.3868**	**0.7529**
	as2&as9	70	0.1399	0.9942	**1.1771**	**0.5417**
	as3	70	0.0525	0.6376	**0.6891**	**0.8043**
	as4_2	70	-0.0062	0.8502	**-0.0608**	**0.6666**
	as7_1	70	-0.0391	0.9103	**-0.3598**	**0.5484**
	as7_2	70	-0.1699	1.0513	**-1.3524**	**0.4511**
	as8_1	70	0.1301	0.6589	**1.6517**	**0.7303**
	as8_2	70	-0.0354	0.9701	**-1.1236**	**0.7549**
	as10	70	-0.1303	0.9273	**0.1565**	**0.5064**
	as12	70	0.0030	0.9805	**0.0254**	**0.4785**
DJ	dj8	70	-0.1231	0.5185	**-1.9860**	**0.8895**
	dj13_15	70	0.0606	0.4898	**1.0354**	**0.8463**
	dj23_24	70	-0.0371	0.5478	**-0.5662**	**0.8536**
	dj28_32&dj44part1	70	0.0467	0.3387	**1.1543**	**0.9500**
	dj44part2&dj47_52	69	-0.0132	0.4046	**-0.2700**	**0.8663**
	dj57&dj59	70	0.0018	0.3510	**0.0418**	**0.9490**
	dj76-80	70	0.0467	1.0306	**0.3791**	**0.5585**
KV	kv1	70	0.0639	0.7473	**0.7149**	**0.7864**
	kv2_6part1	70	-0.0660	0.6520	**-0.8465**	**0.7928**
	kv2_6part2	68	-0.0835	0.5073	**-1.3573**	**0.8762**

MM	mm3_13part1	70	-0.0829	0.6270	**-1.1060**	**0.8078**
	mm55&mm59_1	70	0.1160	0.9158	**1.0595**	**0.6517**
	mm57_1	70	-0.0416	0.9857	**-0.3532**	**0.5377**
	mm57_2	70	0.0543	0.7987	**0.5684**	**0.6828**
	mm57_3	70	-0.0335	0.7485	**-0.3748**	**0.7070**
	mm57_5	70	-0.0037	0.9102	**-0.0338**	**0.6035**
	mm59_2	70	0.0485	0.6945	**0.5841**	**0.7254**
	mm60_1	70	0.0750	0.6301	**0.9957**	**0.8225**
	mm60_2	70	-0.0789	0.7419	**-0.8898**	**0.7698**
	mm3_13(2)&mm15_22	62	-0.1245	0.8585	**-1.1422**	**0.6554**
RM	rm_1v	70	-0.0584	0.4439	**-1.1012**	**0.8903**
	rm_2v	70	-0.0648	0.5438	**-0.9973**	**0.8615**
	rm_3v	70	0.0402	0.3555	**0.9453**	**0.9411**
	rm_4v	50	0.0109	0.2884	**0.2663**	**0.9615**
	rm_g4g5g6	70	-0.0854	0.5054	**-1.4146**	**0.8615**
	rm-v100	70	-0.0058	0.2345	**-0.2082**	**0.9654**
	rm-v101&v105&v106	70	-0.0952	0.3886	**-2.0494**	**0.9226**
	rm-v107&v119&v14	68	-0.1056	0.4542	**-1.9176**	**0.8723**
SL	sl2-3	70	0.0387	0.4264	**0.7594**	**0.9008**
	sl7	69	0.0018	0.5049	**0.0303**	**0.8800**
	sl21_26part1	70	0.0396	0.2277	**1.4533**	**0.9677**
	sl21_26part2	59	0.0593	0.5140	**0.8865**	**0.6561**
	sl28-33part1	70	0.0261	0.5626	**0.3877**	**0.8692**
	sl28-33part2	69	0.0390	0.8199	**0.3954**	**0.6882**
	sl41&48	70	0.0846	0.6751	**1.0481**	**0.8050**
VD	vd11_26part1	70	-0.0188	0.3708	**-0.4250**	**0.9340**
	vd11_26part2	70	0.0557	0.5140	**0.9065**	**0.8941**
	vd11_26part3	70	0.0446	0.3468	**1.0756**	**0.9375**
	vd27_44part1	70	0.0390	0.3958	**0.8237**	**0.9312**
	vd27_44part2	70	-0.0399	0.5174	**-0.6460**	**0.8350**
	vd27_44part3	46	-0.0235	0.3518	**-0.4532**	**0.9041**
VG	vg4	70	0.2077	0.7909	**2.1971**	**0.7404**
	vg7&vg10part1	70	0.0171	0.4492	**0.3177**	**0.9061**
	vg10part2&vg2	70	-0.0930	0.4575	**-1.7010**	**0.8909**
	vg12	70	-0.0357	0.4217	**-0.7084**	**0.9214**
	vg15&18	70	0.0662	0.8727	**0.6349**	**0.7011**
	vg21part1	70	-0.0098	1.0306	**-0.0792**	**0.3985**
	vg21part2	70	0.0831	0.9544	**0.7282**	**0.5861**
VYB	vyb1_3	70	-0.0226	0.6538	**-0.2898**	**0.8318**
	vyb6	68	0.0844	0.2714	**2.5638**	**0.9641**
	vyb7	68	-0.0420	0.2928	**-1.1830**	**0.9608**
	vyb8	70	-0.0224	0.2590	**-0.7241**	**0.9688**
	vyb9_13	69	-0.0386	0.4865	**-0.6599**	**0.8734**
	vyb14&16	70	-0.0364	0.6126	**-0.4974**	**0.7915**
	vyb17_21	70	0.0081	0.2757	**0.2445**	**0.9598**
VM	vk1_3	70	-0.0911	0.5358	**-1.4220**	**0.8330**
	vm4&vm21_23	63	-0.0921	0.7063	**-1.0349**	**0.7612**
	vm5_10	70	0.0375	0.8380	**0.3739**	**0.6113**
	vm11	70	-0.0217	0.9035	**-0.2006**	**0.4771**
	vm12	69	0.0017	0.7195	**0.0194**	**0.7339**
	vm14_17part1	70	-0.0612	0.5144	**-0.9950**	**0.8821**
	vm14_17part2	70	0.0239	0.5684	**0.3525**	**0.8511**
	vm14_17part3	70	-0.0398	0.5921	**-0.5626**	**0.8134**
	vm14_17part4	70	-0.0877	0.5817	**-1.2612**	**0.8172**
	vm14_17part5	70	-0.0178	0.6853	**-0.2173**	**0.7385**
	vm20	70	-0.0223	0.5022	**-0.3711**	**0.8554**
JR	jr1-4_part1	70	-0.1027	0.4777	**-1.7979**	**0.8767**
	jr1-4_part2	70	-0.0034	0.4206	**-0.0671**	**0.9200**
	jr1-4_part3	63	0.0430	0.6655	**0.5126**	**0.7949**
	jr5-6	63	-0.0545	0.5714	**-0.7566**	**0.8232**
	jr7part1	70	0.0046	0.9037	**0.0427**	**0.6141**
	jr8	70	-0.0593	0.8067	**-0.6152**	**0.7200**

The values of t-criterion corresponding to each data set have been calculated using normalized data. Normalization was performed by division the original measurement data by standard deviation. The calculated values of t-criterion, presented in Tables 4, 5, are checked on meeting the inequality:

$$|t| < T_{crit}, \tag{9}$$

where t is calculated value of t-criterion for paired or correlated samples [44], and T_{crit} is critical value of t-statistic [44]:

$$T_{crit} = 1.960 \text{ for } \alpha = 0.05,\ n > 120, \tag{10}$$
$$T_{crit} = 1.997 \text{ for } \alpha = 0.05,\ n = 70, \tag{11}$$
$$T_{crit} = 2.000 \text{ for } \alpha = 0.05,\ n = 60, \tag{12}$$
$$T_{crit} = 2.010 \text{ for } \alpha = 0.05,\ n = 50, \tag{13}$$
$$T_{crit} = 2.021 \text{ for } \alpha = 0.05,\ n = 40, \tag{14}$$

α is the significance level of the test (size of the critical region), n is the number of measurement points.

If the condition (9) is satisfied, the hypothesis on equality of the mean values of measurements under comparison is accepted, otherwise the hypothesis is rejected.

The investigated number of samples is N = 87 and the number of samples that meet the condition (9) in Table 5 is N_+ = 83. The proportion of samples with positive decision is

$$\pi_{N+} = \frac{N_+}{N} = 0.954. \tag{15}$$

The calculated value π_{N+} is more than the proportion of interest $\pi = 0.95$:

$$\pi_{N+} = 0.954 > \pi = 0.95. \tag{16}$$

So, the hypothesis on the coincidence of measurement results is accepted.

2.2.5. Analysis of clinical data

In order to determine the metrological requirements for the deliverable prototype for non-invasive CA monitoring device, the clinical data of this research were analyzed. The results of analysis are shown in Fig. 11 – Fig. 19.

The main results of analysis are as follows:

- in order to obtain correlation coefficient between invasively and non-invasively recorded slow ICP and slow cerebral blood volume waves better than $r \geq 0.9$, it is necessary to perform the monitoring when the amplitude of ICP B waves is more than 3.0 mmHg (Fig. 11). The standard deviation of the correlation coefficient r is also minimal in this case (Fig. 12),

- the same conclusion about the acceptable amplitude of permanent or interminent ICP B waves follows from Fig. 14 concerning the standard deviation of the difference between invasively and non-invasively measured cerebrovascular autoregulation state indices,

- it follows from Fig. 16 that the acceptable ABP slow wave amplitude is more than 5.0 mmHg,

- it has been shown experimentally (Fig. 17, Fig. 18) that the difference between invasively and

non-invasively measured CA indices expressed by the standard deviation σ (Fig. 18) decreases significantly when the autoregulation state has a tendency to be impaired ($r \rightarrow +1.0$) or to be intact ($r \rightarrow -1.0$). In both clinically important cases the random error values expressed by σ are not significant in the clinical practice. The systematic error Δ (Fig. 17, Fig. 19) is also not important in the clinical practice.

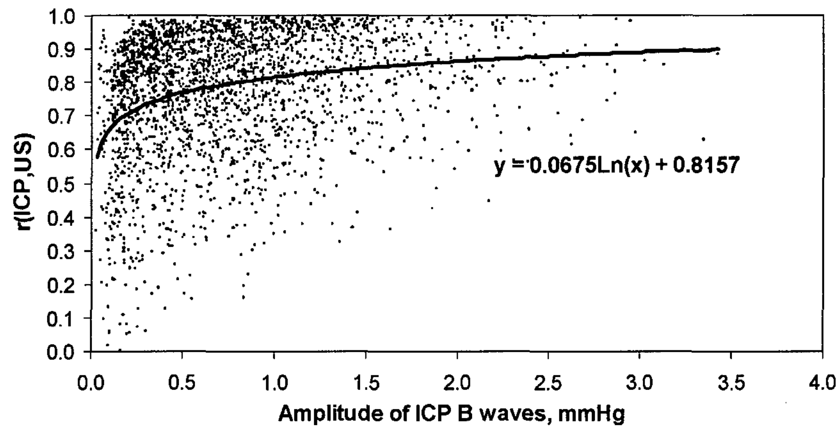


Fig. 11. Mean value of the correlation coefficient between invasive ICP B waves and non-invasively measured intracranial blood volume B waves depending on the amplitude of the ICP B waves (13 patients, 87 hours of simultaneous invasive ICP and non-invasive US monitoring, 2631 experimental data points)

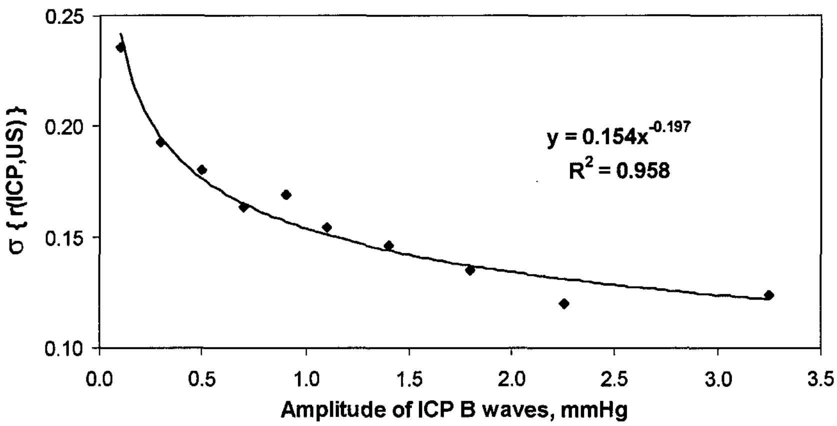


Fig. 12. Standard deviation of the correlation coefficient between invasive ICP B waves and non-invasive ultrasound speed B waves depending on the amplitude of the ICP B waves (13 patients, 87 hours of simultaneous invasive ICP and non-invasive US monitoring)

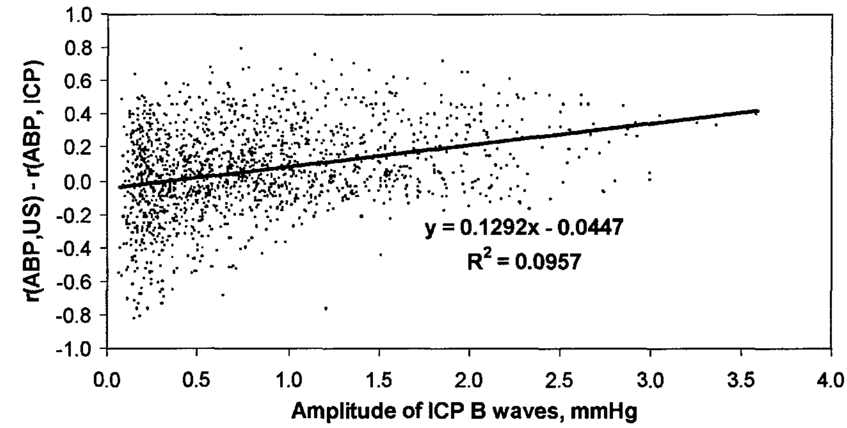


Fig. 13. Mean value of the difference between invasive and non-invasive CA estimating indices depending on the amplitude of ICP B waves (10 patients, 53 hours of simultaneous invasive and non-invasive CA monitoring)

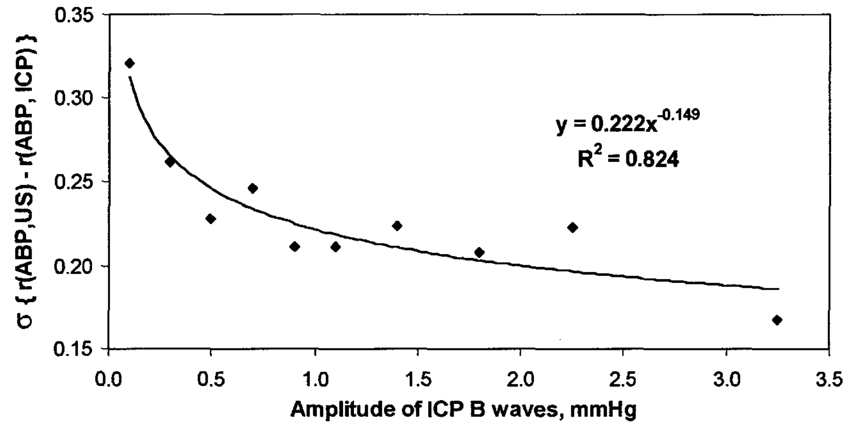


Fig. 14. Standard deviation of the difference between invasive and non-invasive CA estimating indices depending on the amplitude of ICP B waves (10 patients, 53 hours of simultaneous invasive and non-invasive CA monitoring)

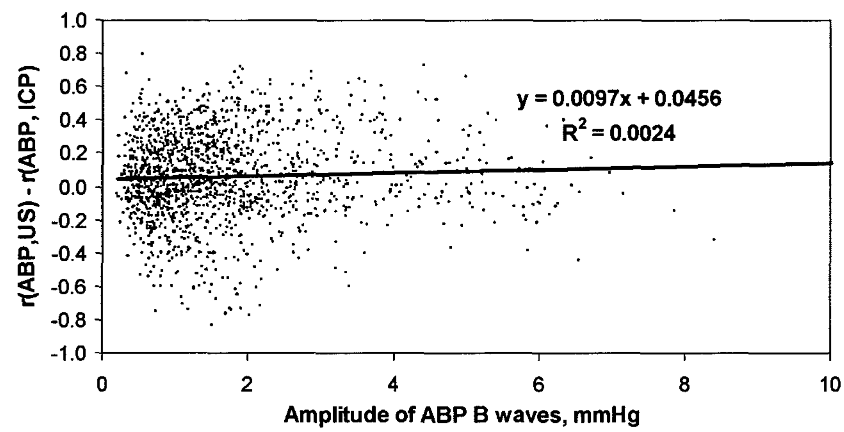


Fig. 15. Mean value of the difference between invasive and non-invasive CA estimating indices depending on the amplitude of ABP B waves (10 patients, 53 hours of simultaneous invasive and non-invasive CA monitoring)

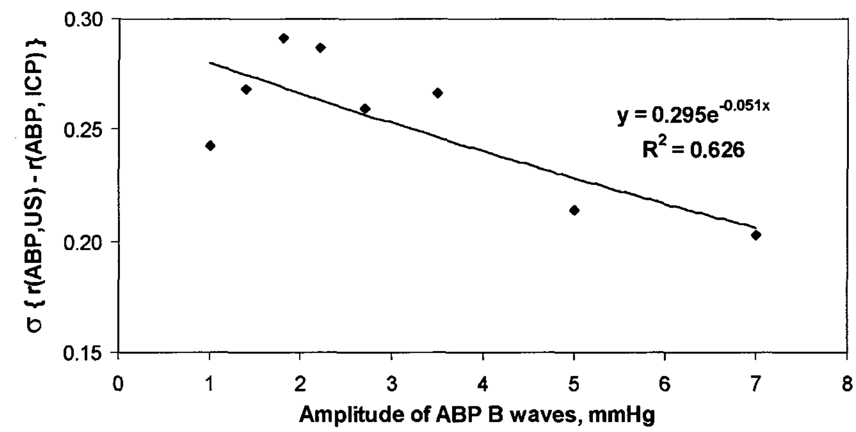


Fig.16. Standard deviation of the difference between invasive and non-invasive CA estimating indices depending on the amplitude of ABP B waves (10 patients, 53 hours of simultaneous invasive and non-invasive CA monitoring)

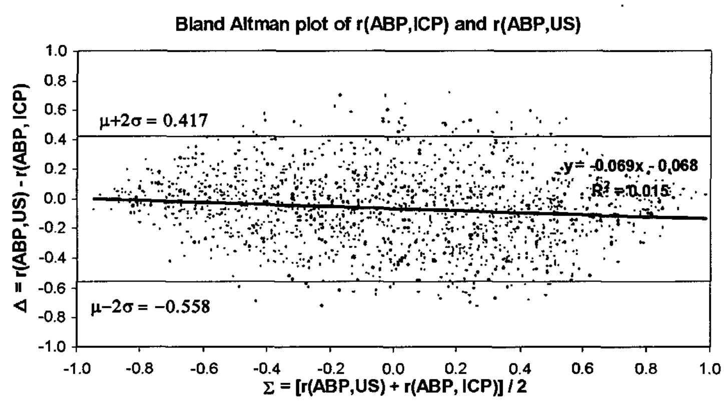


Fig. 17. Estimation of the similarity between invasive and non-invasive CA estimating indices r(ABP, ICP) and r(ABP, US): Bland Altman plot comparing invasive and non-invasive data (10 patients, 53 hours of simultaneous invasive and non-invasive CA monitoring, 1570 experimental data points of CA estimation)

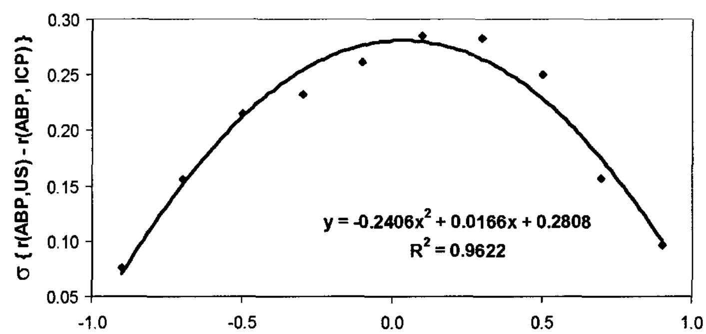


Fig. 18. Standard deviation of the difference between invasive and non-invasive CA estimation indices calculated from Bland Altman plot of r(ABP,ICP) and r(ABP,US) (10 patients, 53 hours of simultaneous invasive and non-invasive CA monitoring)

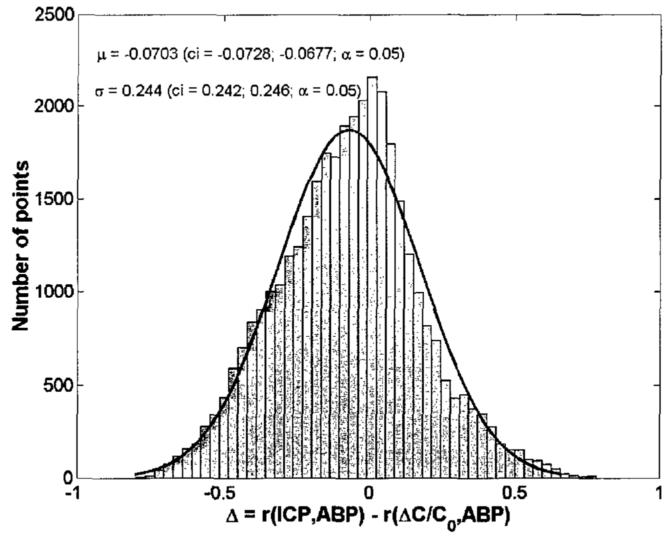


Fig. 19. Estimation of the similarity between invasive and non-invasive CA estimating indices r(ABP, ICP) and r(ABP, US): a) - distribution of differences between the invasive and non-invasive data, b) - Bland Altman plot comparing invasive and non-invasive data (10 patients, 53 hours of simultaneous invasive and non-invasive CA monitoring, 1570 experimental data points of CA estimation)

2.2.6. Conclusion of clinical study

It is proved clinically for the first time that the non-invasive intracranial blood volume slow wave monitor"Vittamed" can be used under ICU conditions for the reliable short- or long-term continuous non-invasive cerebrovascular autoregulation monitoring.

For statistical analysis the same methodology was used as described in paragraphs 1.3.3 – 1.3.5.

Statistically significant estimation (13 patients) shows that the hypothesis of the coincidence of invasively and non-invasively measured ICP and IBV slow wave data is accepted ($\pi>0.95$). Statistically estimated (Bland Altman) difference between invasively and non-invasively recorded intracranial slow waves (SD=0.089, $p=4.5\times10^{-7}$) and the difference between invasively and non-invasively recorded cerebral autoregulation indexes (SD=0.05, $p=1.1\times10^{-6}$) is small enough and such differences are not clinically important.

In this clinical study the statistically significant evidences were obtained at the first time that ultrasonographic time-of-flight technology "Vittamed" could be applied for non-invasive continuous cerebrovascular autoregulation monitoring.

2.3. TECHNOLOGICAL REQUIREMENTS FOR NON-INVASIVE CEREBROVASCULAR AUTOREGULATION MONITOR PROTOTYPE DEVELOPMENT

The requirements for the development and design of the new more advanced deliverable prototype device for cerebrovascular autoregulation monitoring are as follows:

- to include into a cerebrovascular autoregulation monitor a non-invasive arterial blood pressure (ABP) monitoring (replacement of invasive ABP line) transducer for slow ABP waves monitoring with the possibility to monitor slow ABP waves with amplitudes from 1 mmHg to 10 mmHg,

- to improve the hardware and software solutions in order to increase the accuracy of an automatic compensation of the influence of blood flow in the extracranial tissues inside the acoustic path . It is necessary to identify automatically the quality of the received ultrasonic echo signals from the internal surfaces of skull bones and dura mater.

- to improve the software solutions for automatic ultrasonic signal quality identification on-line and to improve an automatic adjustment of the zero crossing points in the received signals in order to determine the artifacts during the cerebrovascular autoregulation state monitoring,

- to improve the software solutions for the estimation of the shape and amplitude of measured slow intracranial blood volume B waves and slow ABP waves with the necessary accuracy ,

- to improve a mechanical frame for ultrasonic transducers fixation on the human head in order to increase comfort for the patient under monitoring,

- to create the data transfer protocol and software solutions for connection of ultrasonic transducers with “black box”-type interfacing hardware which will be connected to a notebook PC for data processing and non-invasive cerebrovascular autoregulation state indication on-line in numerical form.

3. KEY RESEARCH ACCOMPLISHMENTS
(Performance period 1 October 2001 – 1 October 2002)

1.0. Approved statement of work: non-invasive ICP measurement through the human eye.

1.5. Perform clinical evaluation of the prototype and the clinical study.

Accomplishment: the prototype has been evaluated in ICU. Clinical study of invasive and non-invasive measurement of absolute ICP has been performed in ICU. 57 simultaneous invasive and non-invasive absolute ICP measurements have been performed on 10 ICU patients following Clinical Research protocol No. 99124006. The hypothesis on zero value of differences between invasive and non-invasive absolute ICP measurements under comparison was accepted after analysis of statistically significant clinical data of this study.

2.0. Approved statement of work: non-invasive ICP / volume real - time monitoring.

2.5. Perform clinical evaluation of the prototype and the clinical study.

Accomplishment: the prototype has been evaluated in ICU. Clinical study of invasive and non-invasive slow blood volume wave and cerebrovascular autoregulation monitoring has been performed in ICU. 87 hours of simultaneous invasive and non-invasive monitoring have been performed on 13 ICU patients following Clinical Research protocol No. 99124006. The hypothesis on the coincidence between invasive and non-invasive monitoring data under comparison was accepted after analysis of statistically significant clinical data of this study.

Resume: All the approved statements of the work for the second year of this study have been successfully accomplished.

4. REPORTABLE OUTCOMES

The key research accomplishments were orally presented by Dr. A. Ragauskas at the conferences ATACCC 2001 (Fort Walton Beach, September, 2001) and ATACCC 2002 (Fort Sant Pete Beach, September, 2002). The abstracts of presentations are attached as an Appendix D to this report.

5. CONCLUSIONS

1. The clinical results of this study show that the prototype two-depth TCD device for absolute ICP measurement can be used in ICU environment. Our clinical study (57 measurements, 10 ICU patients with traumatic brain injuries) of the absolute ICP measurement below and above the critical level of ICP = 20.0 - 25.0 mmHg applying PI as a balance indicator shows that the systematic error of non-invasive absolute ICP meter is negligible and that is the only meter which do not need the individual calibration of the system "individual patient – non-invasive ICP meter".

2. The hypothesis on zero value of differences between invasive and non-invasive absolute ICP measurements under comparison was accepted after analysis of statistically significant clinical data of this study.

3. A prototype time-of-flight device for cerebrovascular autoregulation state non-invasive monitoring has been designed and successfully tested in ICU following Clinical Research Protocol No. 9912 4006, AIBS No. 990135, HSSRB Log No. A – 9676. 87 hours of simultaneous invasive and non-invasive ICP slow wave monitoring sessions were performed in ICU on patients with traumatic brain injuries. 53 one hour sessions of cerebrovascular autoregulation continuous monitoring were performed on ICU patients. Simultaneous invasive and non-invasive recording of slow ICP and slow intracranial parenchymal blood volume waves show a high correlation between invasively and non-invasively measured slow waves. The achieved highest correlation values were $R_{C/V}$ = 0.92 ... 0.94 during one-hour continuous monitoring session.

4. In order to obtain correlation coefficient between invasively and non-invasively recorded slow ICP and slow cerebral blood volume waves better than $r \geq 0.9$, it is necessary to perform the monitoring when the amplitude of ICP B waves is more than 3.0 mmHg (Fig. 11). The standard deviation of the correlation coefficient r is also minimal in this case (Fig. 12). The same conclusion about the acceptable amplitude of permanent or interminent ICP B waves follows from Fig. 14 concerning the standard deviation of the difference between invasively and non-invasively measured cerebrovascular autoregulation state indices. It follows from Fig. 16 that the acceptable ABP slow wave amplitude is more than 5.0 mmHg. It has been shown experimentally (Fig. 17, Fig. 18) that the difference between invasively and non-invasively measured CA indices expressed by the standard deviation σ (Fig. 18) decreases significantly when the autoregulation state has a tendency to be impaired ($r \rightarrow +1.0$) or to be intact ($r \rightarrow -1.0$). In both clinically important cases the random error values expressed by σ are not significant in the clinical practice. The systematic error Δ (Fig. 17, Fig. 19) is also not important in the clinical practice.

5. Statistically significant estimation (13 patients, 87 hours of continuous invasive and non-invasive monitoring) shows that the hypothesis of the coincidence of invasively and non-invasively measured ICP and IBV slow wave data is accepted ($\pi>0.95$). Statistically estimated (Bland Altman) difference between invasively and non-invasively recorded intracranial slow waves (SD=0.089, $p=4.5\times10^{-7}$) and the difference between invasively and non-invasively recorded cerebral autoregulation indexes (SD=0.05, $p=1.1\times10^{-6}$) is small enough and such differences are not clinically important.

6. In this clinical study the statistically significant evidences were obtained at the first time that ultrasonographic time-of-flight technology "Vittamed" could be applied for non-invasive continuous cerebrovascular autoregulation monitoring.

7. All the approved statements of the work for the second final year of this study have been successfully accomplished.

6. REFERENCES

1. D. Teres, R. Brown, and S. Lemshaw, ``Predicting mortality of intensive care unit patients: the importance of coma," Crit. Care Med., vol. 10, pp. 86-95, 1982.
2. D. Levy, ``Prognosis in nontraumatic coma," Ann. Int. Med., vol. 94, pp. 293-301, 1981.
3. P.Wolf, ``An overview of the epidemiology of stroke," Stroke, vol. 21, pp. 4-6, 1990.
4. R. Burger, G. H. Vince, J. Meixensberger, K. Roosen. "Hypothermia influences time course of intracranial pressure, brain temperature, EEG and microcirculation during ischemia-reperfusion", Neurological Research, vol. 20, Suppl. 1, pp. S52-S60, 1998.
5. Ragauskas A., Daubaris G. A method and apparatus for non-invasively deriving and indicating of dynamic characteristics of the human and animal intracranial media // US Patent 5388583, 1995; Int. Patent Application PCT/IB94/00293, Intern. Publication WO95/06435, 1995; European Patent 0717606, 1999.
6. Piper I, "Intracranial pressure and elastance": In Head Injury. Ed. PL Reilly and R. Bullock, Chapman & Hall, London, 1997, pp. 101-120.
7. Miller JD, et al, "ICP monitoring: Indications and techniques", In: Narayan, RK: Neurotrauma, pp. 429-444, 1996,
8. J.D. Pickard, M. Czosnyka,"Management of raised intracranial pressure," Journal of Neurol Neurosurg Psychiatry, 56, pp 845-58, 1993.
9. H Kushiwaki et al,"Human dural thickness measured by ultrasonographic method: reflection of intracranial pressure," Journal Ultrasound Med, 16:11, pp. 725-30, 1997.
10. M.S. Salman, "Can intracranial pressure be measured non-invasively", The Lancet, 350:8, pp. 1367, 1997.
11. T. Ueno, R. Ballard et al, "Non-invasive measurement of intracranial pressure pulsation using ultrasound", Aviation Space and Environmental Medicine, 68:7, pp. 646, 1997.
12. N.L. Johnson, F.C. Leone. Statistics and Experimental Design in Engineering and Physical Sciences. John Wiley & Sons, 1977.
13. B.R. Kirkwood. Essentials of Medical Statistics. Blackwell Science Ltd, 1988.
14. US Patents No. No. 5 720 290, 5 840 018, 5 919 144, 5 993 398, 6 117 089, 6 150 941, 6 179 773, 6 231 509, 6 328 694, 6 364 849, 6 371 916, 6 375 607, 6 387 051, 6 422 990, 6 086 533, 6 231 509, 6 309 354.17
15. Czosnyka M, Pickard J, Whitehouse H, Piechnik S (1992). The hyperaemic response to a transient reduction in cerebral perfusion pressure. Acta Neurochir 115, 90-97.
16. Czosnika M, Smielewski P, Kirkpatrick P, Menon DK, Pickard JD (1996). Monitoring of cerebral autoregulation in head-injured patients. Stroke 27, 1829-1834.
17. Czosnika M, Smielewski P, Kirkpatrick P, Laing RJ, Menon D, Pickard JD (1997). Continuous assessment of the cerebral vasomotor reactivity in head injury. Neurosurgery 41, 11-19 (also private communication with Dr M Czosnyka).
18. Lemaire JJ, Boire JY, Chazal J, Irthum B (1994). A computer software for frequential analysis of slow intracranial pressure waves. Comput Methods Programs Biomed, 42, 1-14.
19. Lemaire JJ, Irthum B, Chazal J, Boire JY (1994). Statistical analysis of ICP and frequential analysis of slow waves during the course of subarachnoid haemorrhage following arterial aneurysm rupture: effects of vasospasm. ICP IX. Eds. Nagai H, Kamiya K, Ishii S. Springer-Verlag Berlin Heidelberg New York London Paris Tokyo Hong Kong Barcelona Budapest. 184-188.
20. Lemaire JJ, Chazal J, Gutknecht JL, Picard P, Irthum B, Boire JY (1994). Effects of acute compliance fluctuation on slow ICP waves: frequential aspects. ICP IX. Eds. Nagai H, Kamiya K, Ishii S. Springer-Verlag Berlin Heidelberg New York London Paris Tokyo Hong Kong Barcelona Budapest. 498-501.
21. Lemaire JJ, Burlat JF, Khalil T, Chabane A, Irthum B, Chazal J (1998). Computer software for frequential monitoring of intracranial pressure (and related signals) slow waves. Intracranial Pressure and Neuromonitoring brain Injury. Eds. Marmarou A, Bullock R,

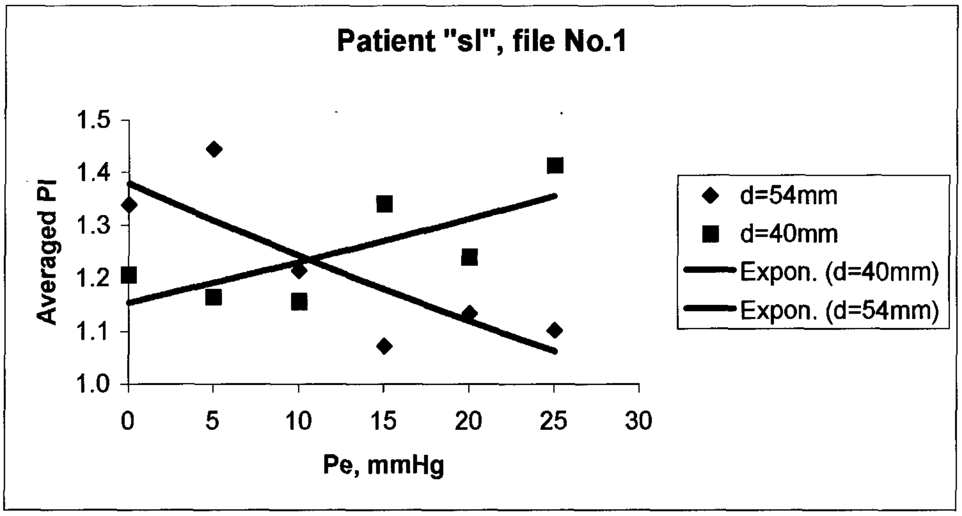
Avezaat C, Baethmann A, Becker D, Brock M, Hoff J, Nagai H, Reulen HJ, Teasdale G. Acta Neurochirugica [suppl] 71: 388.

22. Lemaire JJ, Khalil T, Cervenansky F, Boire JY, Sinardet D, Schmidt E, Fischer-Lokou D, Irthum B, Chazal J, Bonnard-Gougeon M (1998). Nouvelle méthode d'étude clinique de la vasomotricité cérébrale: approche de l'autorégulation dynamique ?Abstract XX^{èmes} journées de l'Association de Neuro-anesthésie réanimation de langue Française. Paris, Sorbonne 19-20 novembre 1998 (also private communication with Prof. JJ Lemaire).
23. Ursino M, Giammarco PD (1991). A mathematical model of the relationship between cerebral blood volume and intracranial pressure changes: the generation of plateau waves. Ann Biomedical Engineer 19, 15-42 (also private communication with Prof. M Ursino).
24. Sahuquillo J, Amoros S, Santos S, Poca MA, Valenzuela H, Baguena M, Garnacho A. False autoregulation (pseudoregulation) in patients with severe head injury. Its importance in CPP management. Acta Neurochir (2000) [Suppl] 76: 485-490.
25. Czosnyka M., Smielewski P., Piechnik S., Steiner L. A., Pickard J. D. and Chir M. Cerebral autoregulation following head injury // J. Neurosurg., vol. 95, pp. 756-763, Nov. 2001.
26. Czosnyka M., Smielewski P., Piechnik S. and Pickard J. D. Clinical significance of cerebral autoregulation // Acta Neurochir., suppl. 81, pp. S117-S119, June 2002.
27. Czosnyka M., Pickard J., Whitehouse H. and Piechnik S. The hyperaemic response to a transient reduction in cerebral perfusion pressure // Acta Neurochir., vol. 115, pp. 90-97, 1992.
28. Czosnyka M., Smielewski P., Kirkpatrick P., Menon D. K. and Pickard J. D. Monitoring of cerebral autoregulation in head-injured patients // Stroke, vol. 27, pp. 1829-1834, 1996.
29. Czosnyka M., Smielewski P., Kirkpatrick P., Laing R. J., Menon D. K. and Pickard J. D. Continuous assessment of the cerebral vasomotor reactivity in head injury // Neurosurg., vol. 41, pp. 11-19, 1997.

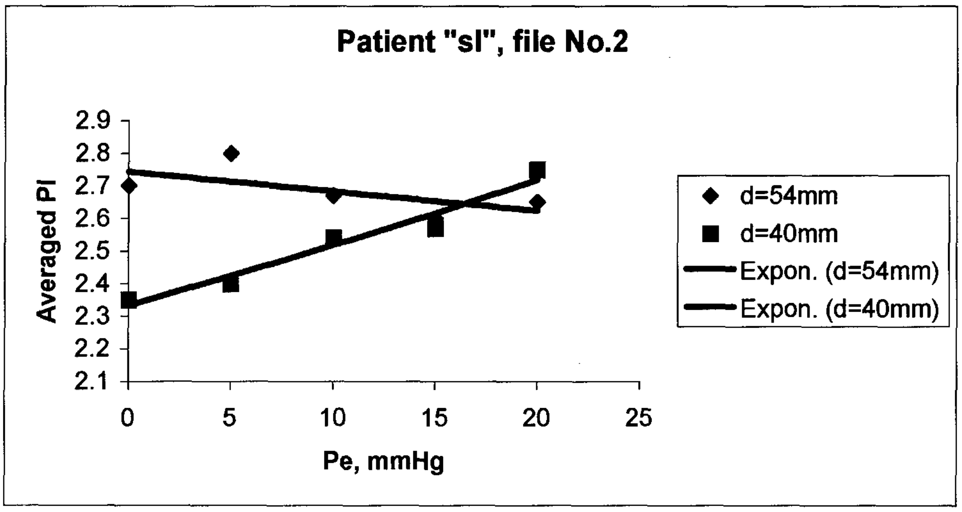
APPENDIXES

APPENDIX A

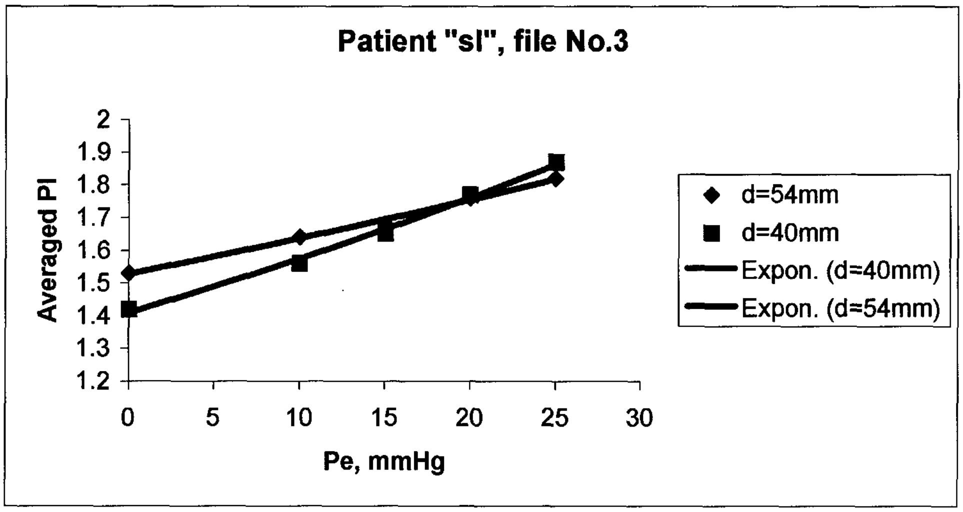
CLINICAL RESULTS OF NON-INVASIVE ABSOLUTE INTRACRANIAL PRESSURE MEASUREMENT



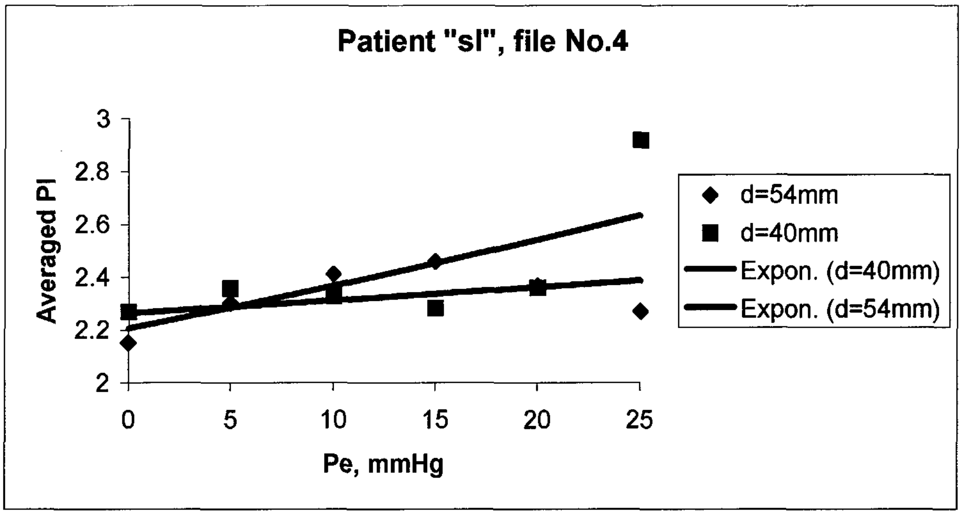
Trial No. 1. Invasive ICP=8.5mmHg, non-invasive ICP=11.5mmHg



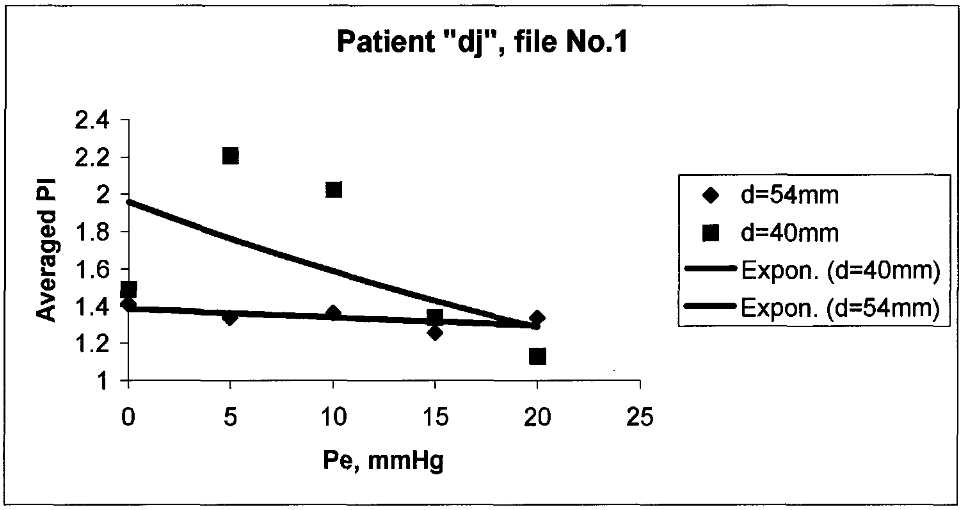
Trial No. 2. Invasive ICP=16mmHg, non-invasive ICP=16mmHg



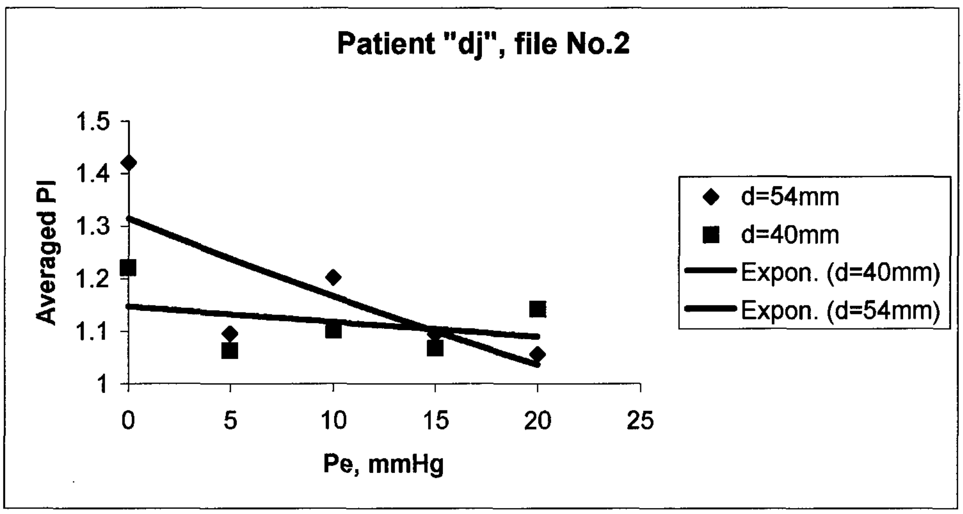
Trial No. 3 Invasive ICP=14mmHg, non-invasive ICP=18mmHg



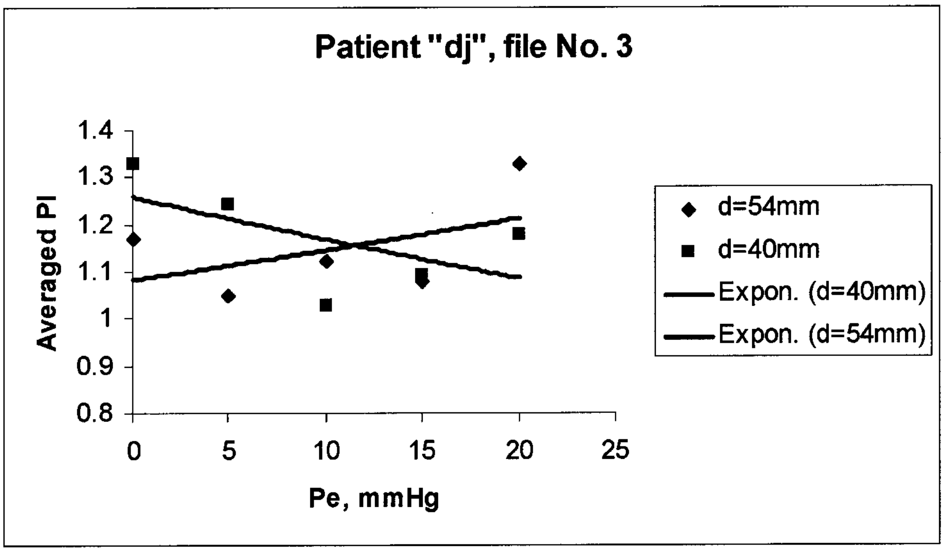
Trial No. 4 Invasive ICP=6mmHg, non-invasive ICP=6mmHg



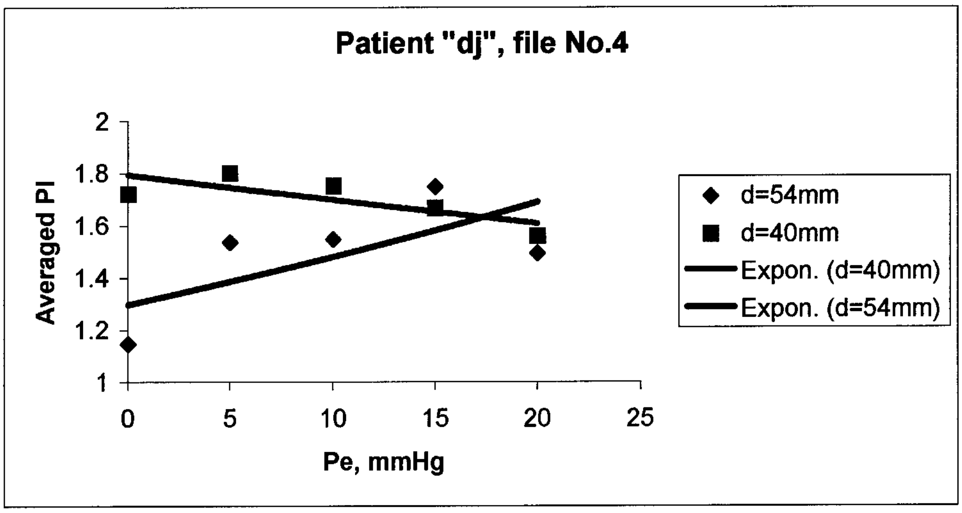
Trial No. 5 Invasive ICP=8mmHg, non-invasive ICP=19mmHg



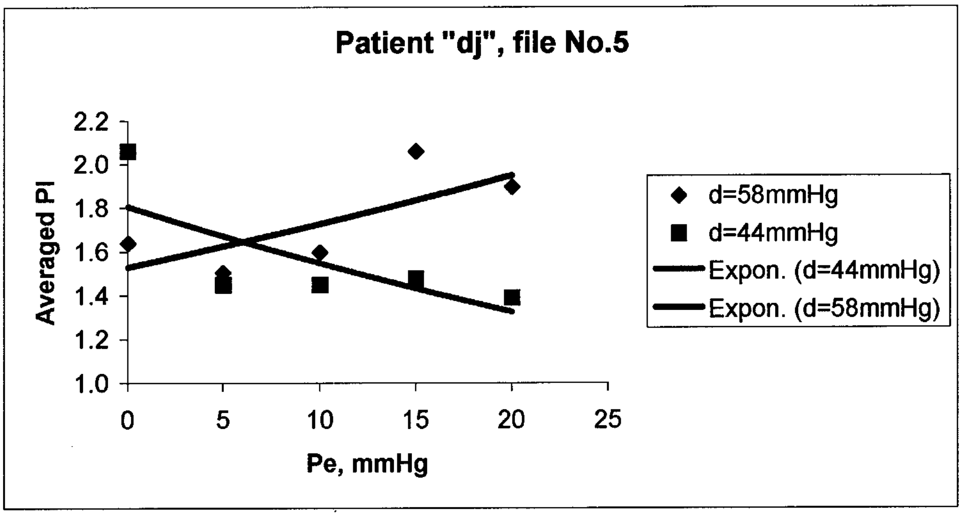
Trial No. 6 Invasive ICP=12mmHg, non-invasive ICP=14.5mmHg



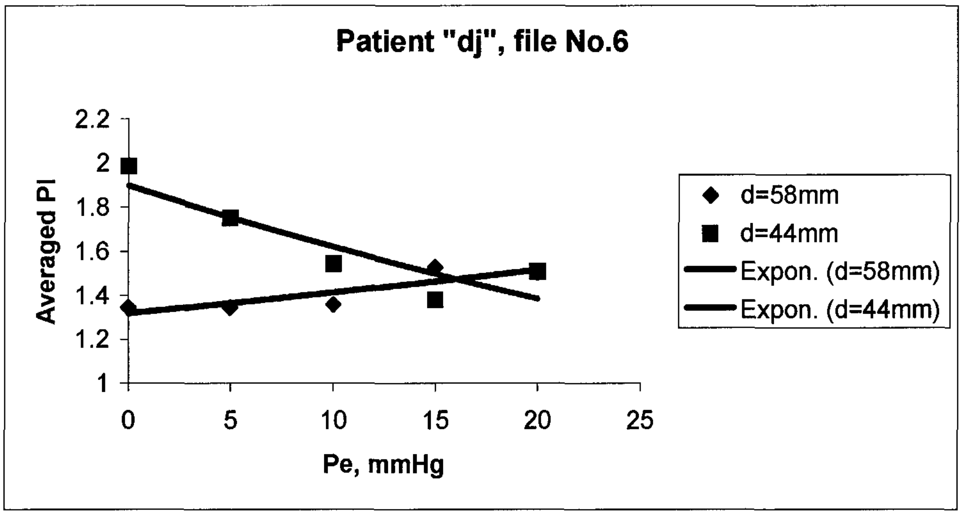
Trial No. 7 Invasive ICP=14mmHg, non-invasive ICP=12mmHg



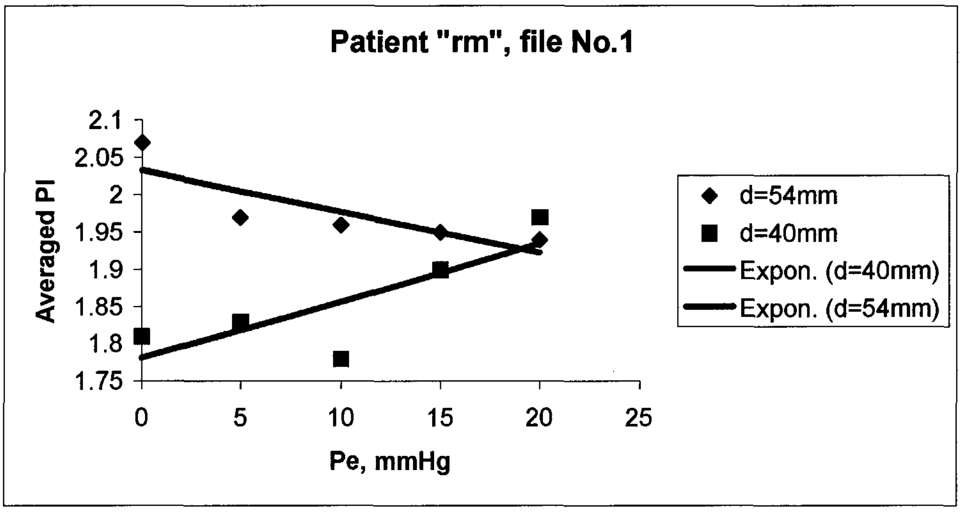
Trial No. 8 Invasive ICP=16mmHg, non-invasive ICP=16.5mmHg



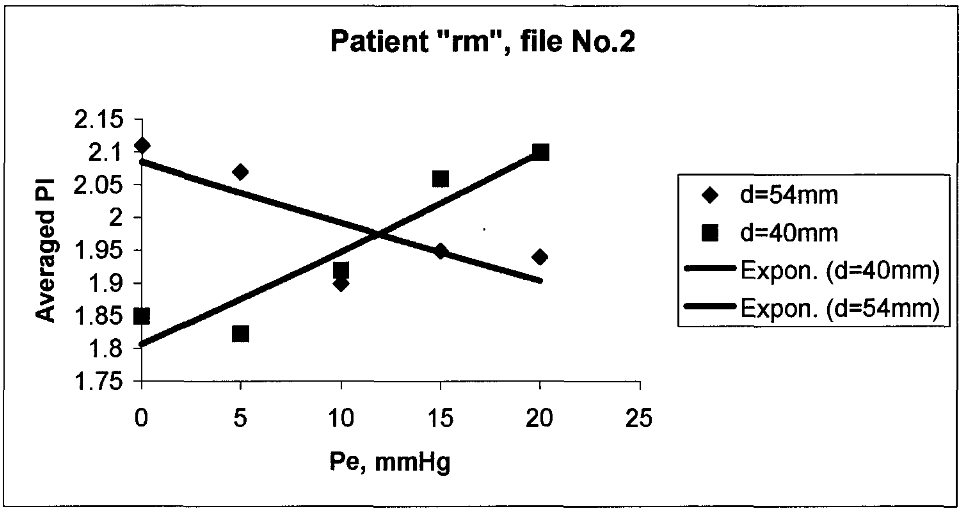
Trial No. 9 Invasive ICP=10mmHg, non-invasive ICP=6mmHg



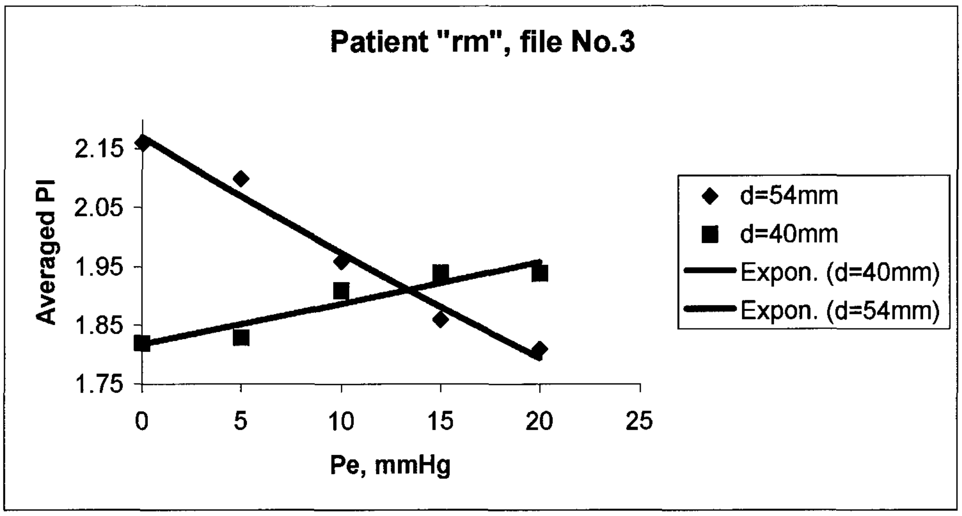
Trial No. 10 Invasive ICP=5mmHg, non-invasive ICP=16mmHg



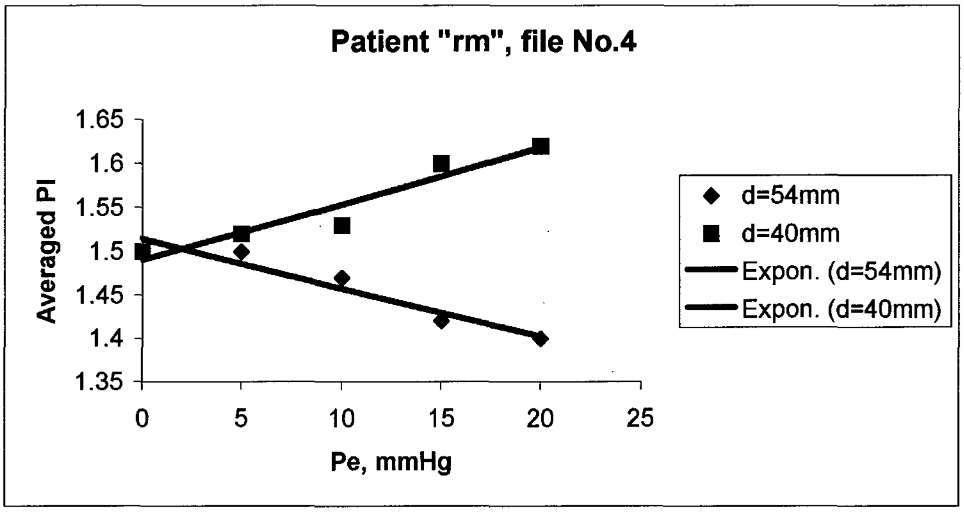
Trial No. 11 Invasive ICP=8mmHg, non-invasive ICP=19.5mmHg



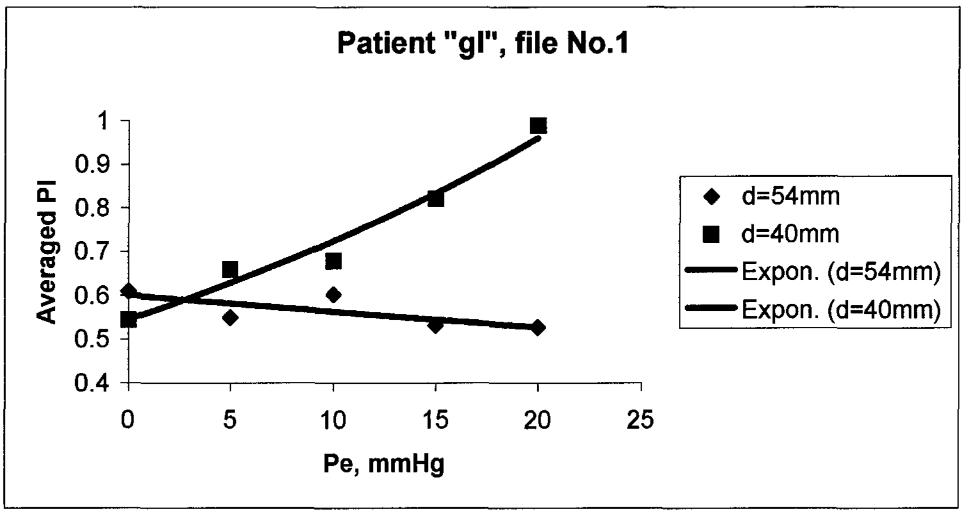
Trial No. 12 Invasive ICP=10mmHg, non-invasive ICP=11.5mmHg



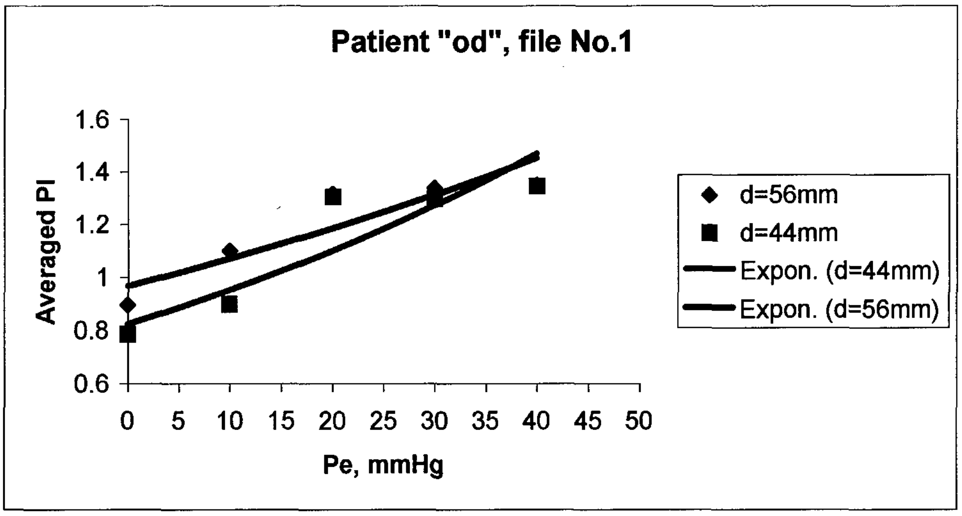
Trial No. 13 Invasive ICP=6mmHg, non-invasive ICP=13mmHg



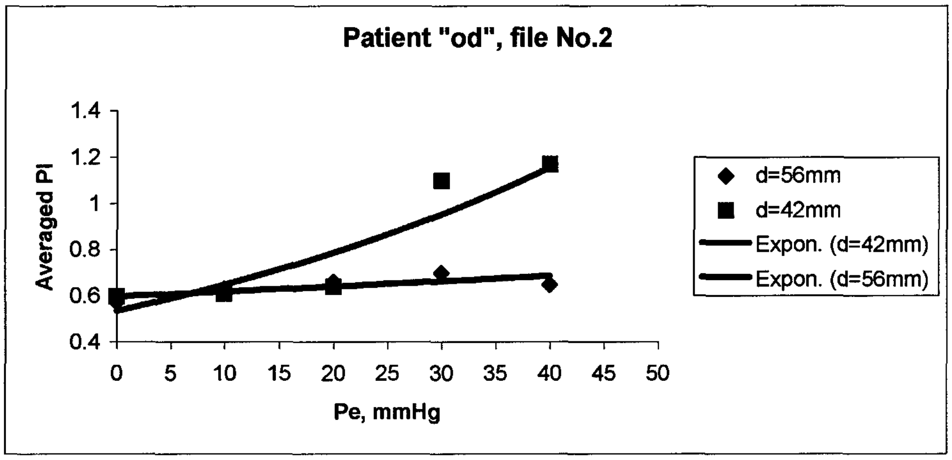
Trial No. 14 Invasive ICP=4mmHg, non-invasive ICP=2mmHg



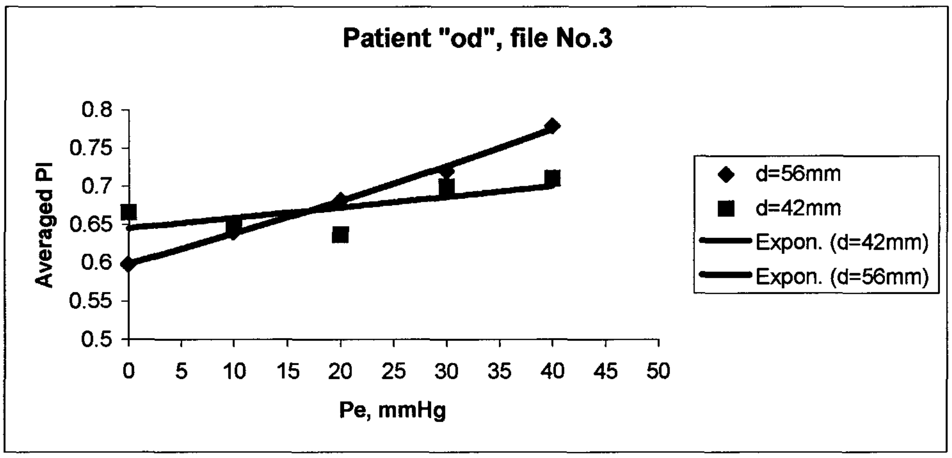
Trial No. 15 Invasive ICP=6mmHg, non-invasive ICP=3mmHg



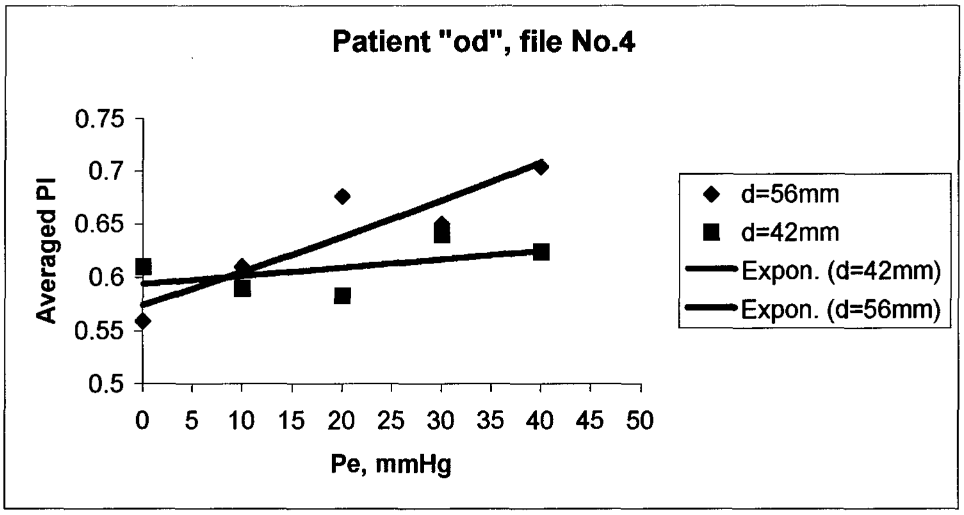
Trial No. 16 Invasive ICP=24mmHg, non-invasive ICP=34mmHg



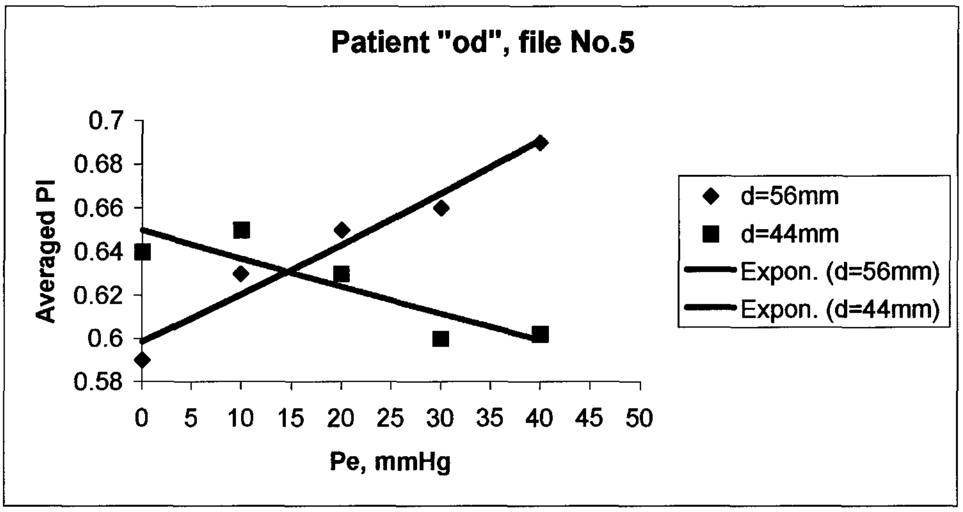
Trial No. 17 Invasive ICP=20mmHg, non-invasive ICP=6mmHg



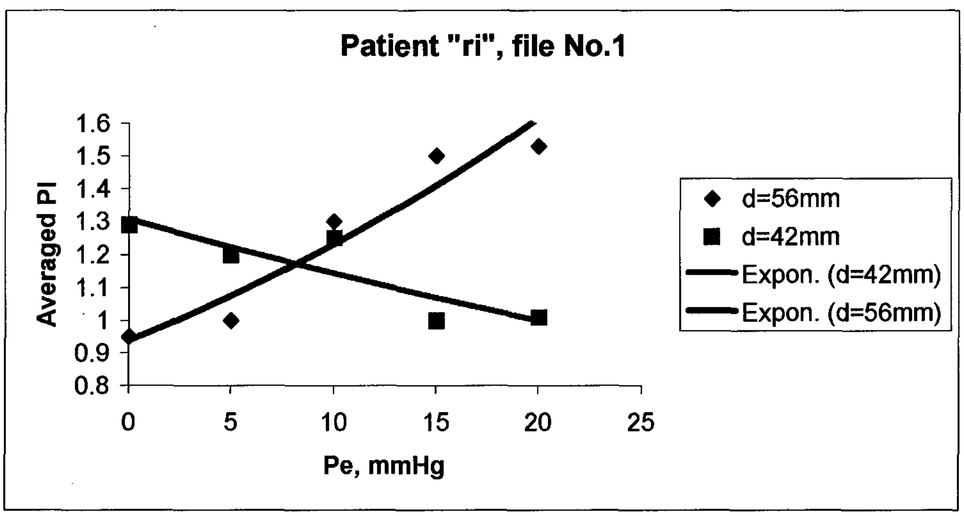
Trial No. 18 Invasive ICP=18mmHg, non-invasive ICP=17mmHg



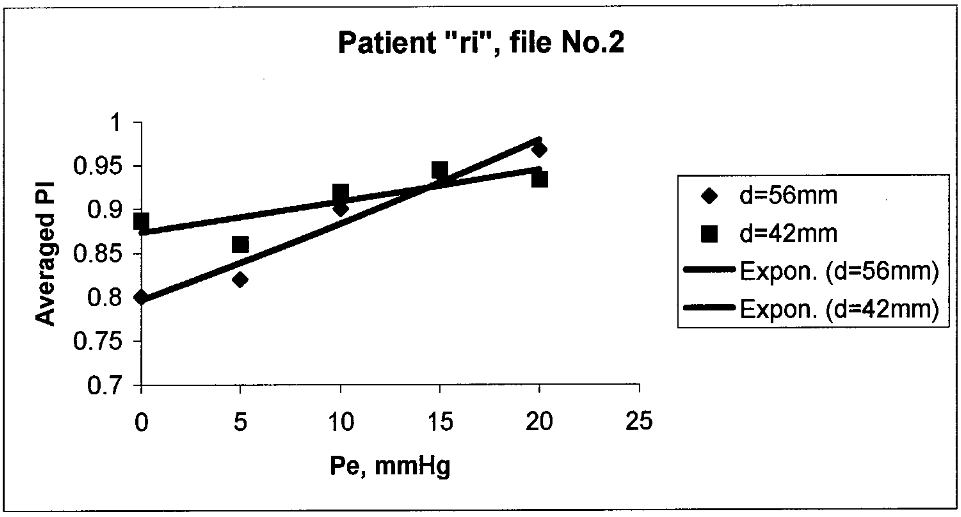
Trial No. 19 Invasive ICP=16mmHg, non-invasive ICP=9mmHg



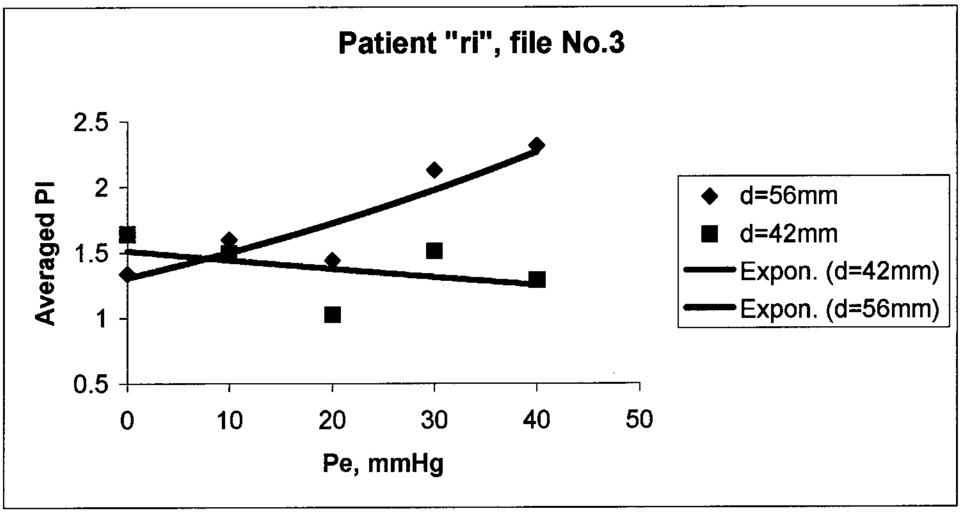
Trial No. 20 Invasive ICP=14mmHg, non-invasive ICP=15mmHg



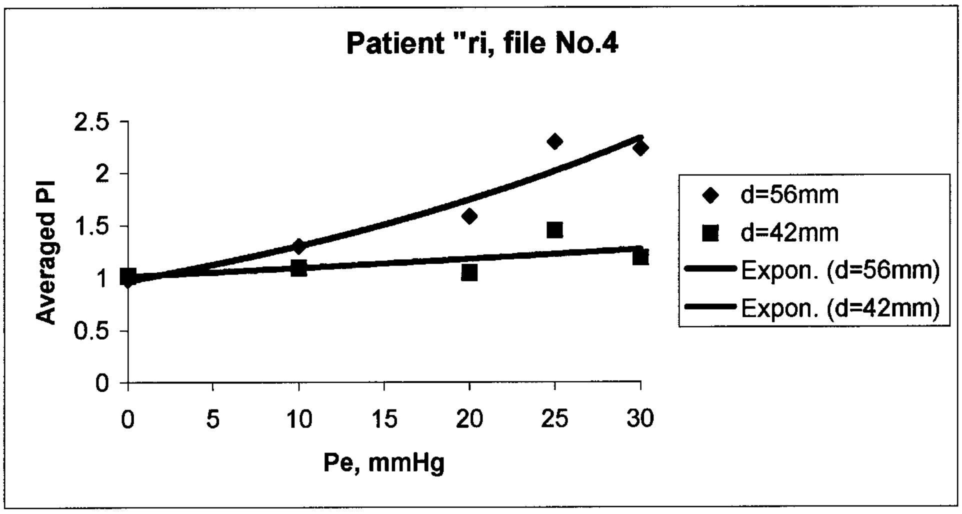
Trial No. 21 Invasive ICP=11mmHg, non-invasive ICP=8mmHg



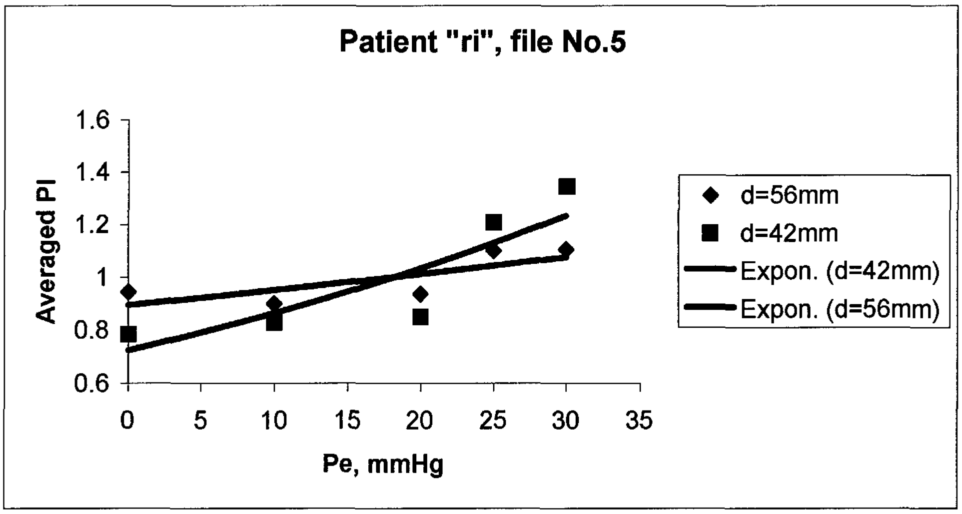
Trial No. 22 Invasive ICP=13mmHg, non-invasive ICP=14mmHg



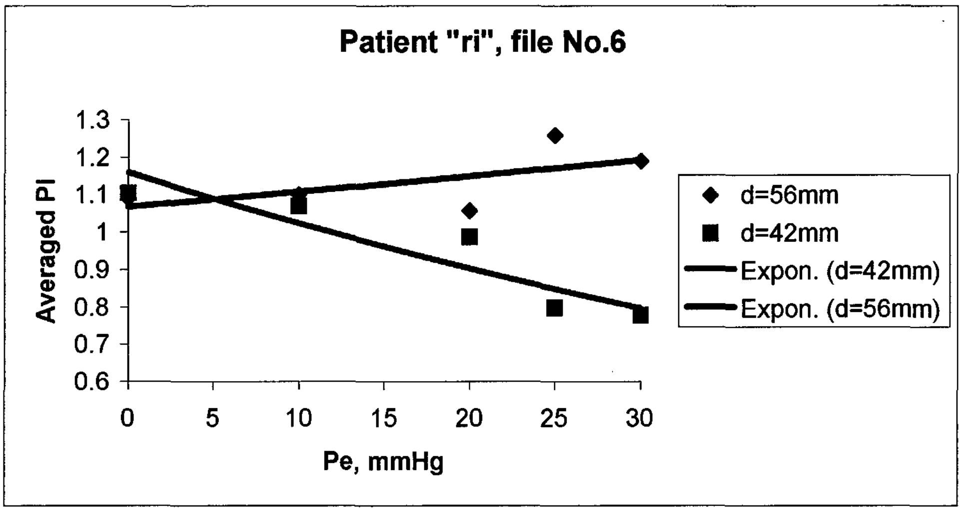
Trial No. 23 Invasive ICP=15mmHg, non-invasive ICP=8mmHg



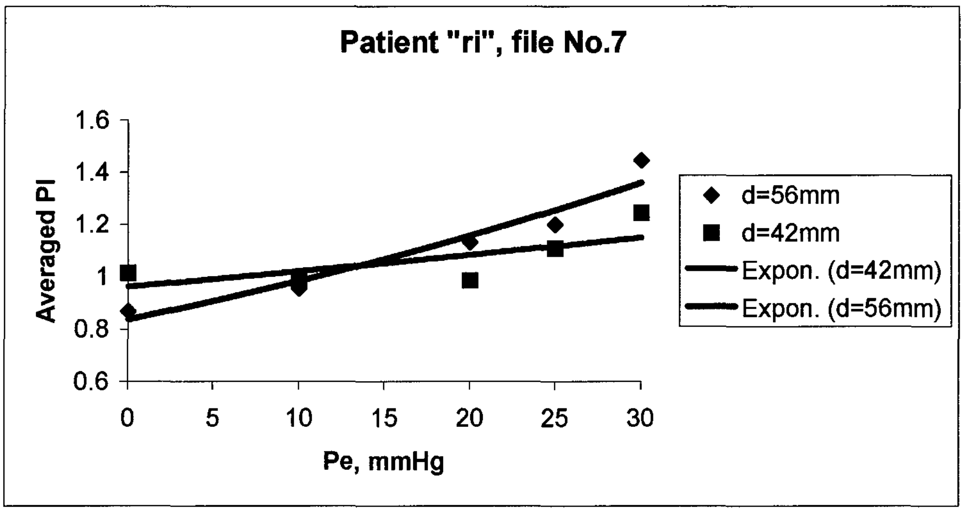
Trial No. 24 Invasive ICP=8mmHg, non-invasive ICP=2mmHg



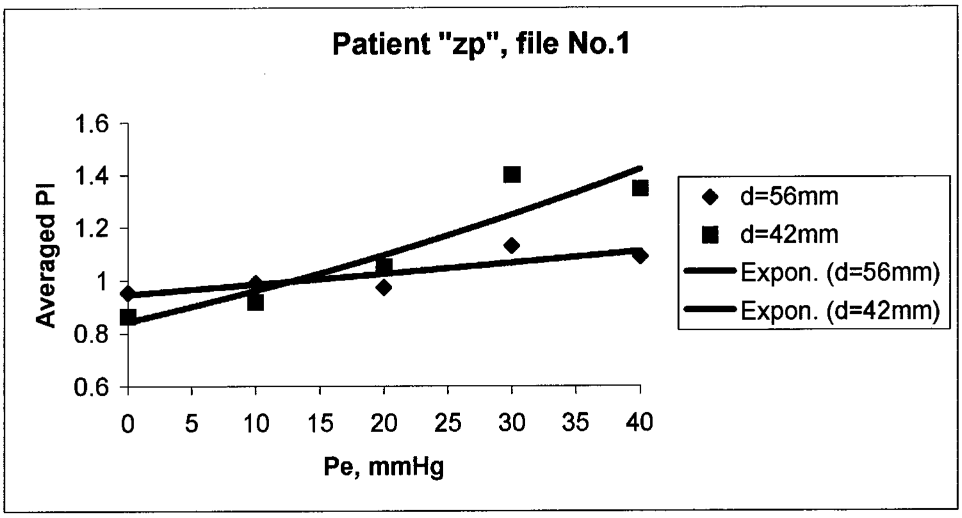
Trial No. 25 Invasive ICP=12mmHg, non-invasive ICP=19mmHg



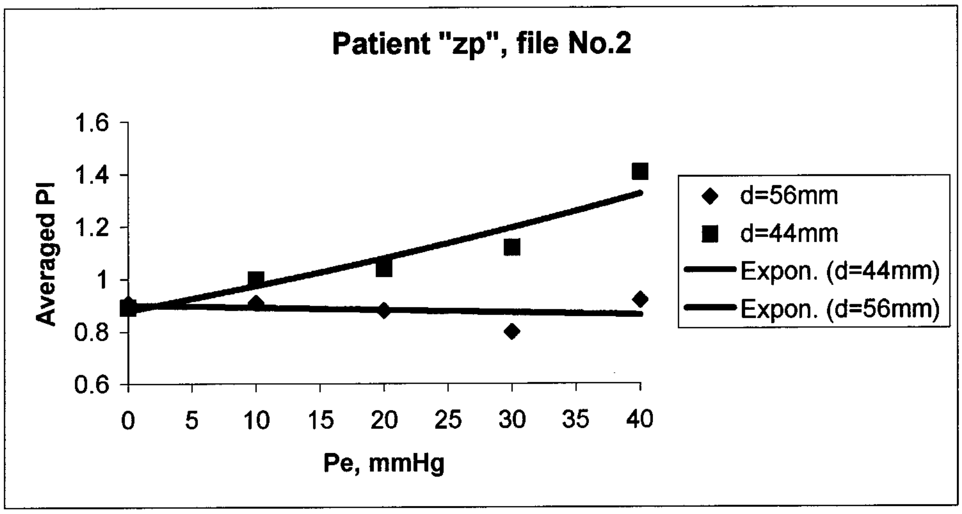
Trial No. 26 Invasive ICP=7mmHg, non-invasive ICP=5mmHg



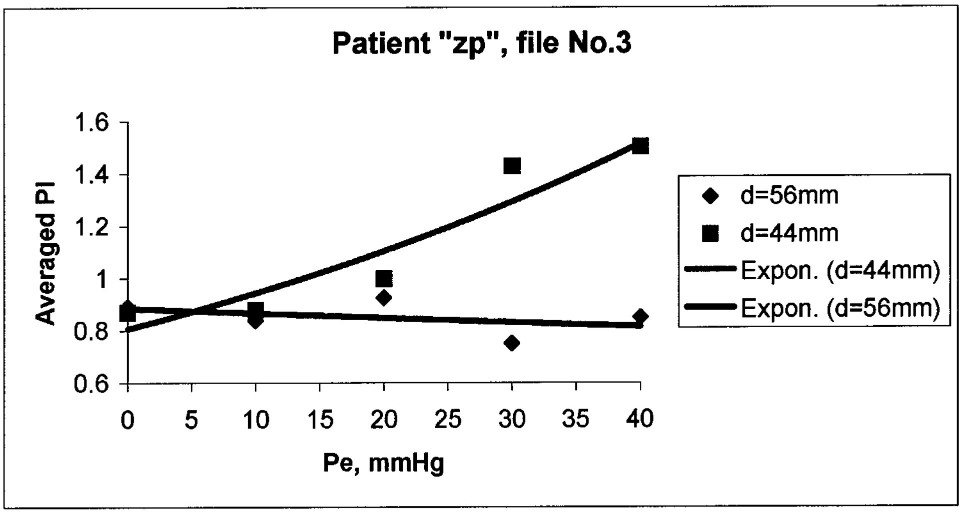
Trial No. 27 Invasive ICP=9mmHg, non-invasive ICP=13mmHg



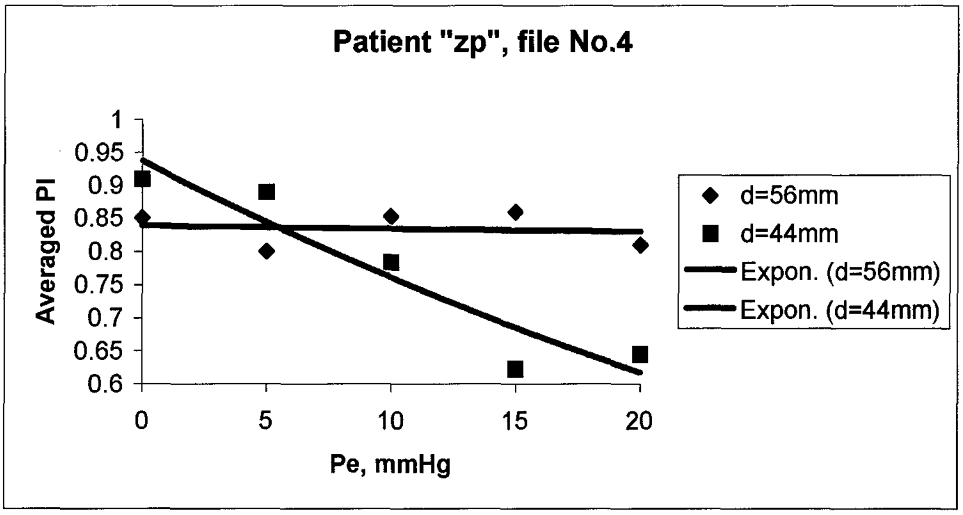
Trial No. 28 Invasive ICP=15mmHg, non-invasive ICP=12mmHg



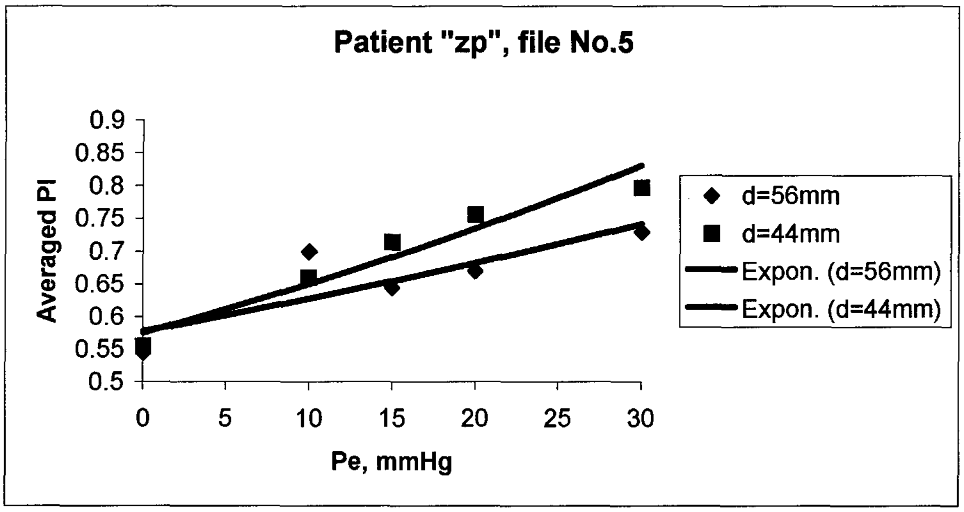
Trial No. 29 Invasive ICP=10mmHg, non-invasive ICP=3mmHg



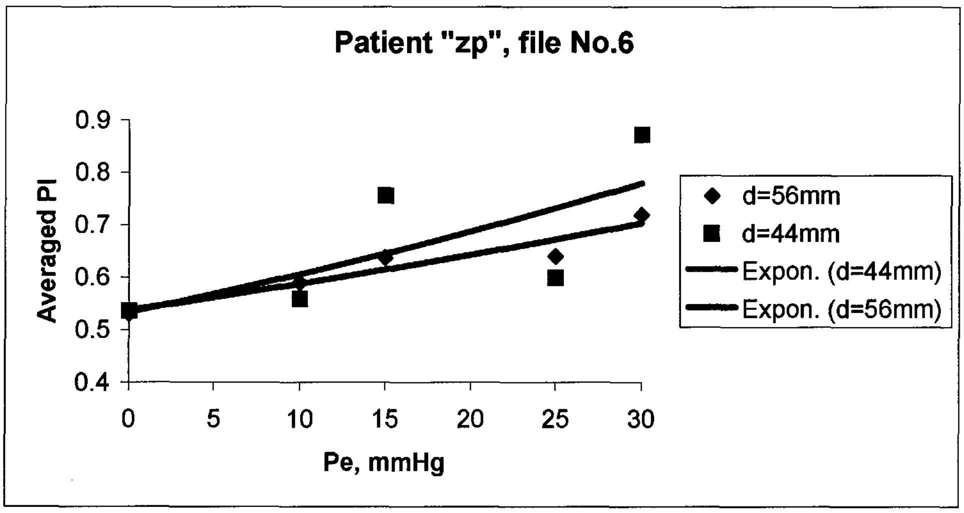
Trial No. 30 Invasive ICP=12mmHg, non-invasive ICP=6mmHg



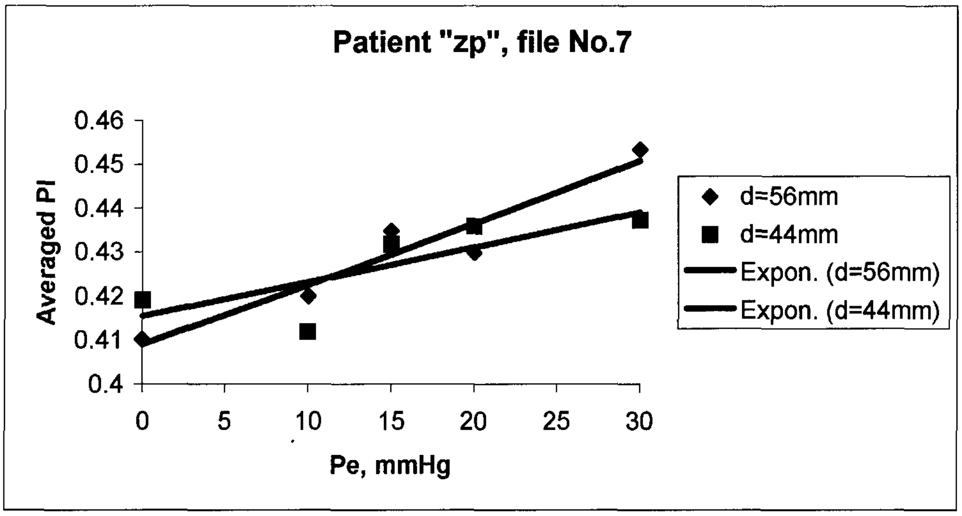
Trial No. 31 Invasive ICP=5mmHg, non-invasive ICP=5mmHg



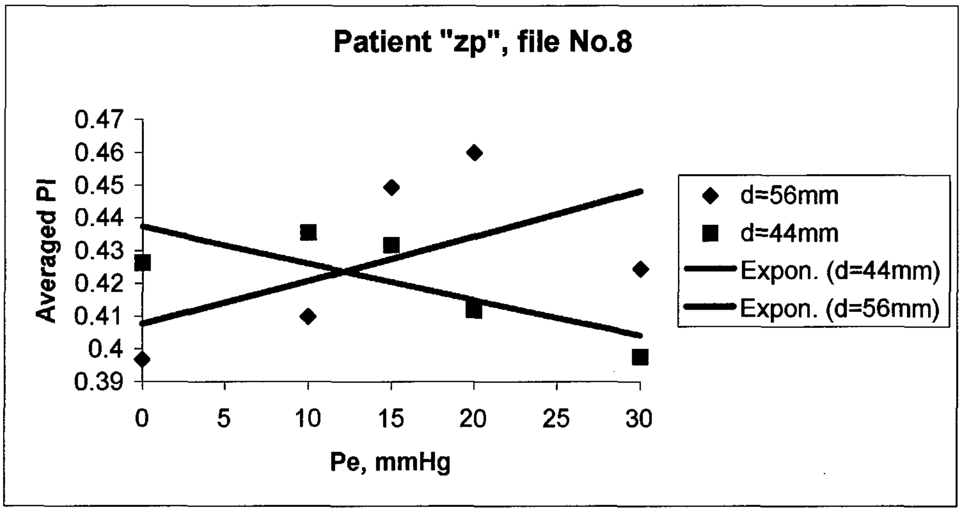
Trial No. 32 Invasive ICP=8mmHg, non-invasive ICP=0.5mmHg



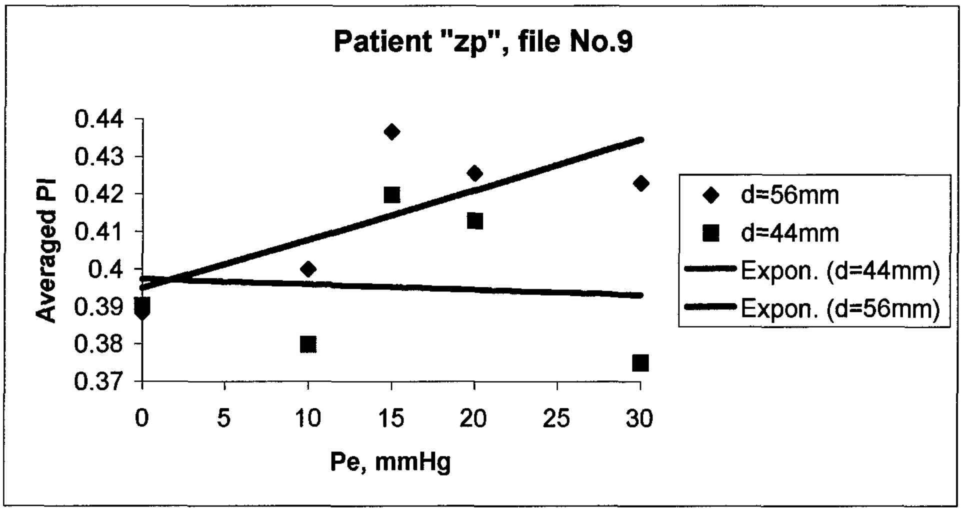
Trial No. 33 Invasive ICP=11mmHg, non-invasive ICP=1mmHg



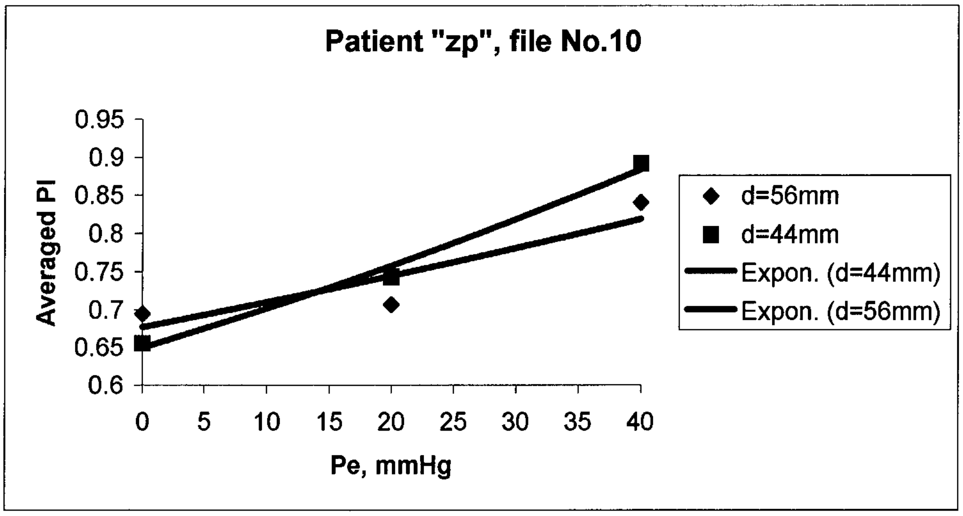
Trial No. 34 Invasive ICP=7mmHg, non-invasive ICP=11mmHg



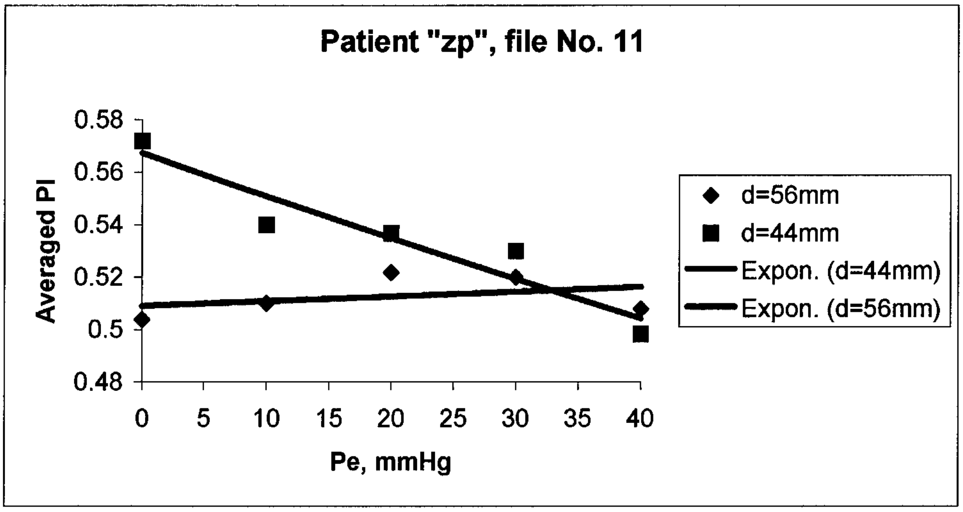
Trial No. 35 Invasive ICP=9mmHg, non-invasive ICP=12mmHg



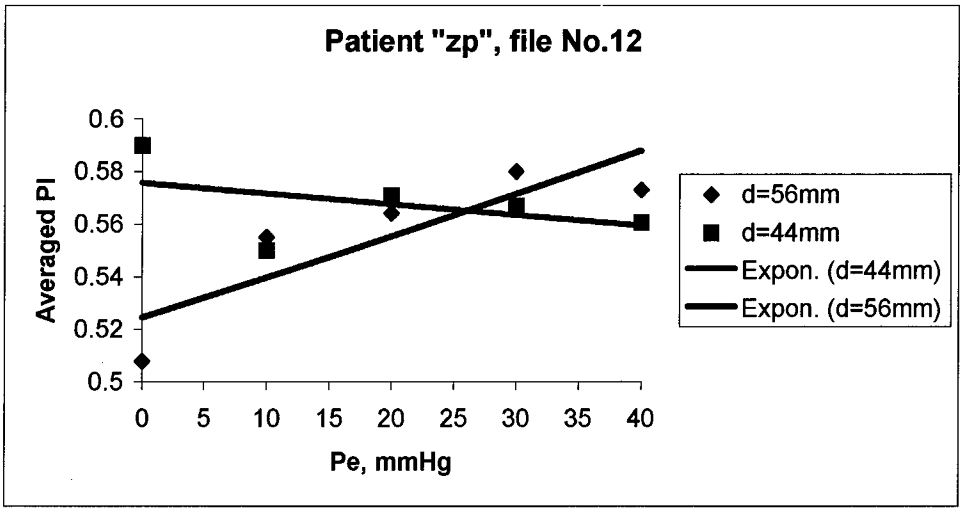
Trial No. 36 Invasive ICP=5mmHg, non-invasive ICP=3mmHg



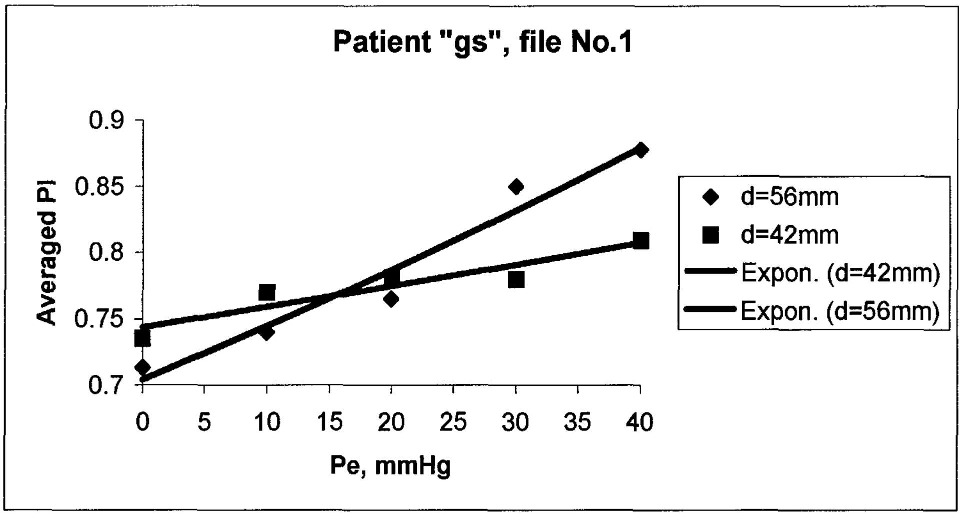
Trial No. 37 Invasive ICP=24mmHg, non-invasive ICP=14mmHg



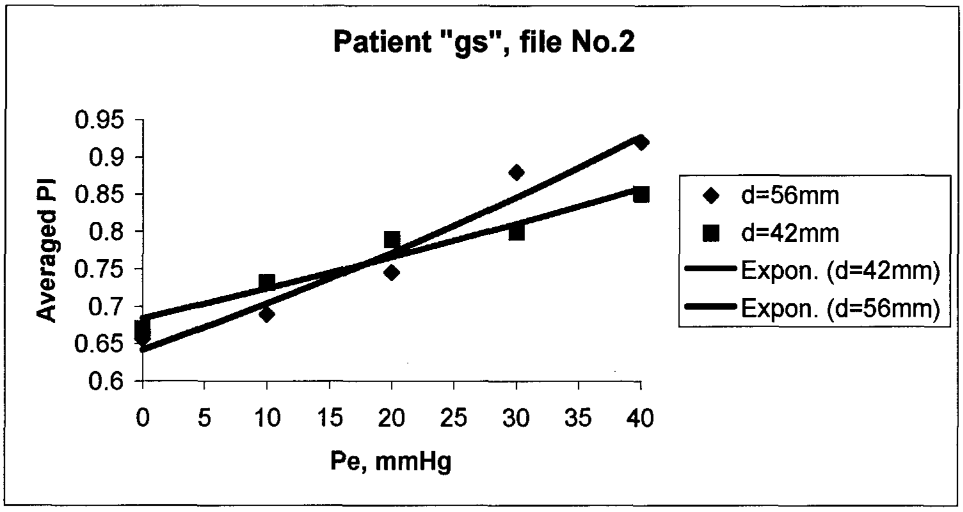
Trial No. 38 Invasive ICP=26mmHg, non-invasive ICP=32mmHg



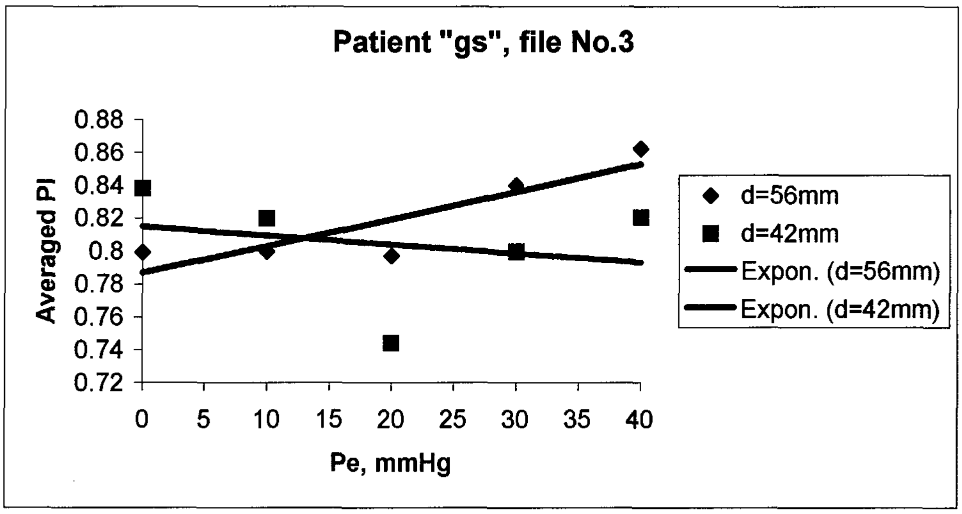
Trial No. 39 Invasive ICP=29mmHg, non-invasive ICP=27mmHg



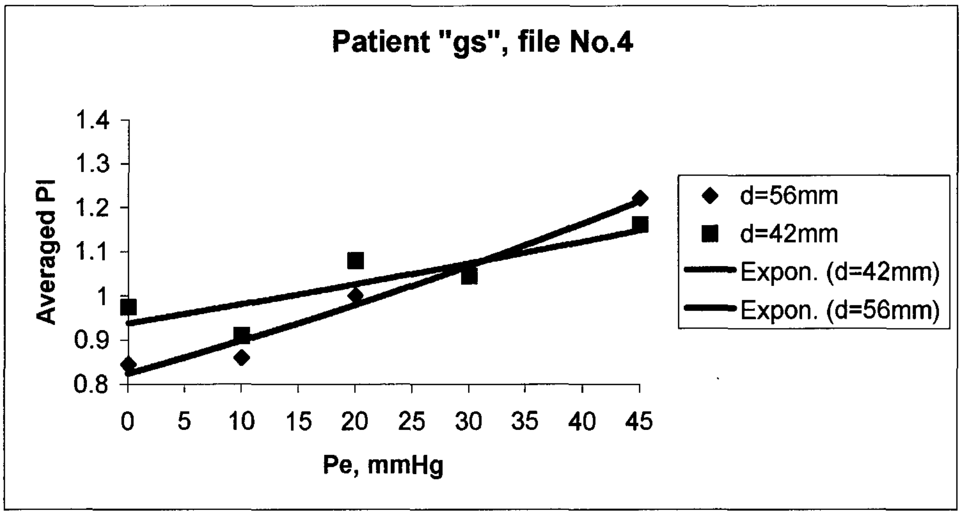
Trial No. 40 Invasive ICP=14mmHg, non-invasive ICP=16mmHg



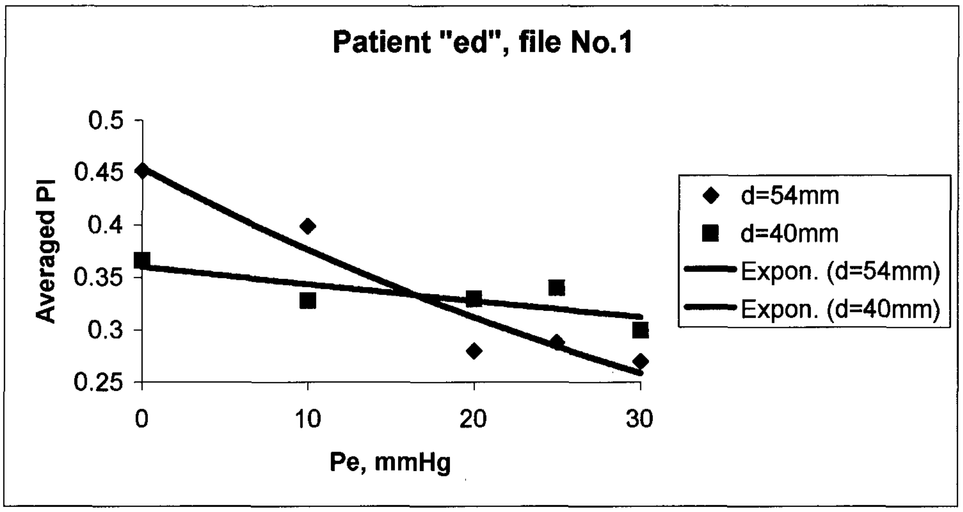
Trial No. 41 Invasive ICP=16mmHg, non-invasive ICP=19mmHg



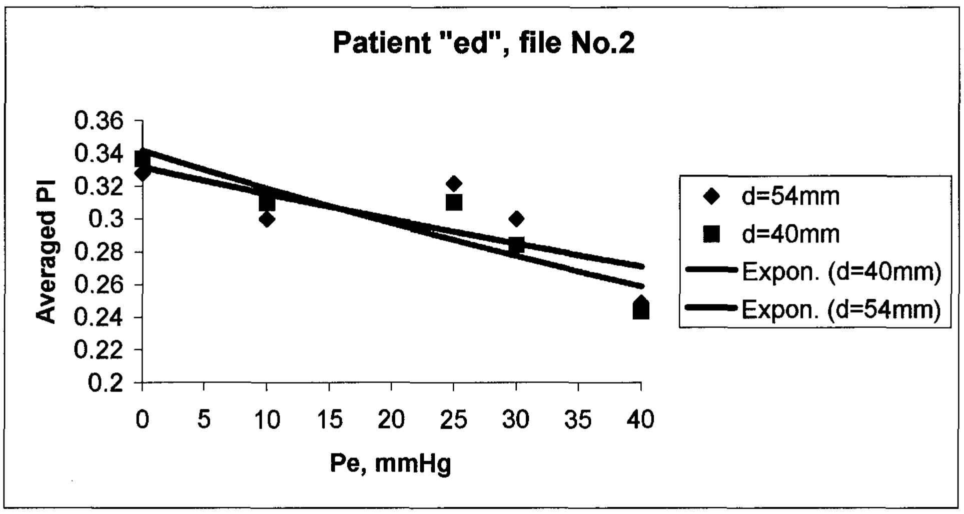
Trial No. 42 Invasive ICP=18mmHg, non-invasive ICP=12mmHg



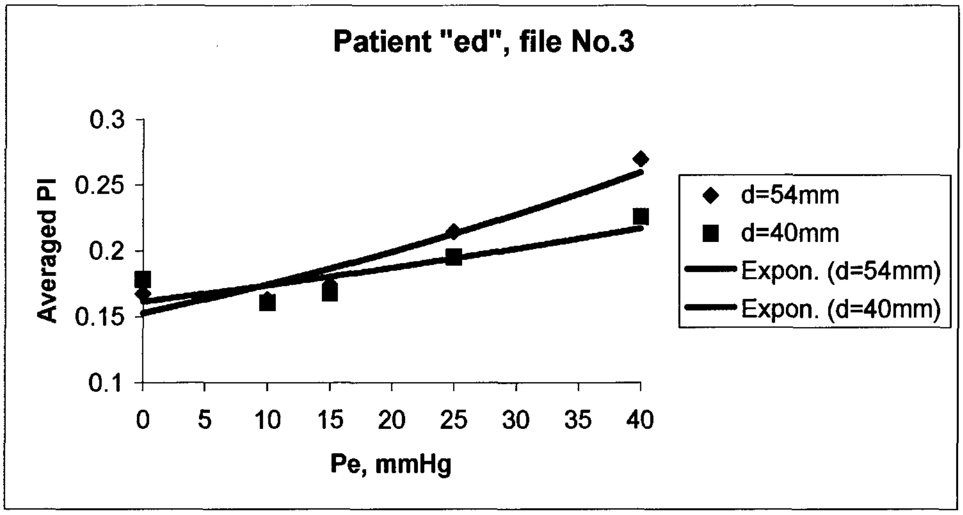
Trial No. 43 Invasive ICP=22mmHg, non-invasive ICP=31mmHg



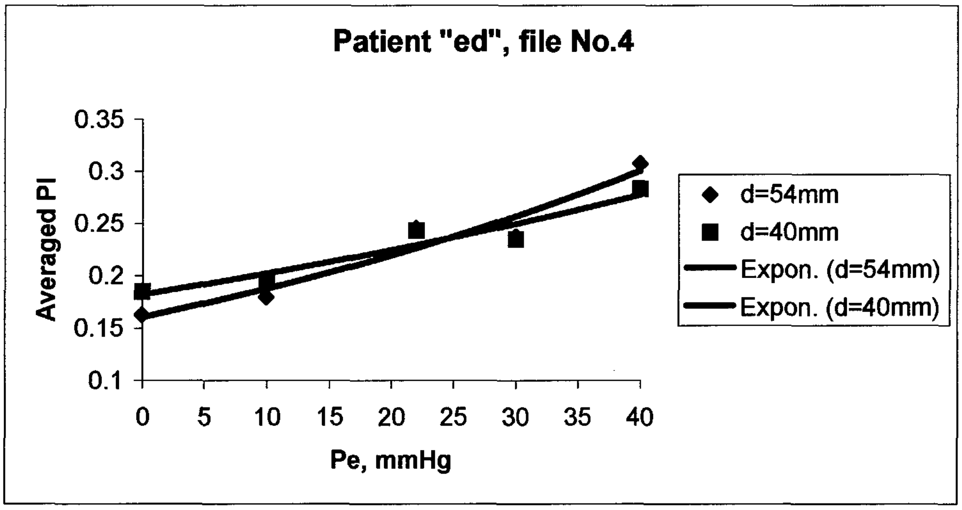
Trial No. 44 Invasive ICP=24mmHg, non-invasive ICP=17mmHg



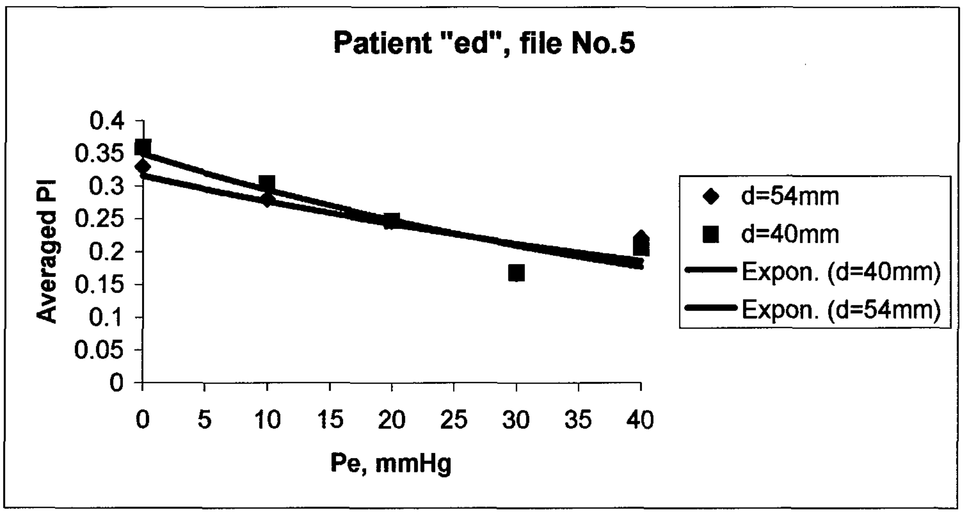
Trial No. 45 Invasive ICP=20mmHg, non-invasive ICP=15mmHg



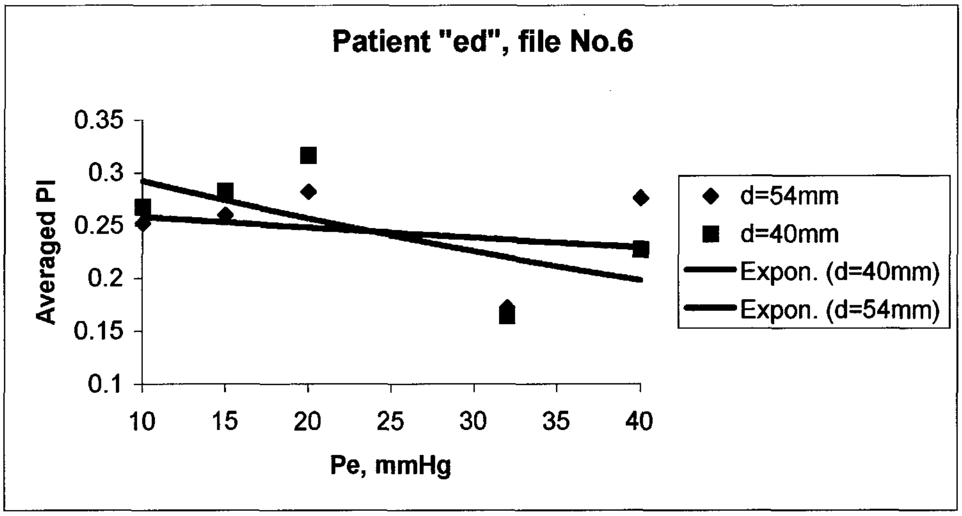
Trial No. 46 Invasive ICP=23mHg, non-invasive ICP=10mHg



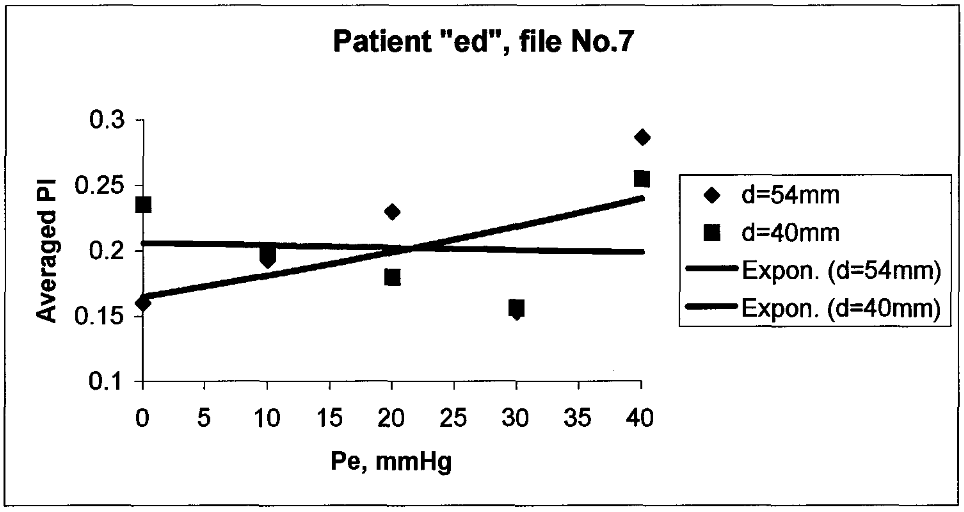
Trial No. 47 Invasive ICP=27mHg, non-invasive ICP=24mHg



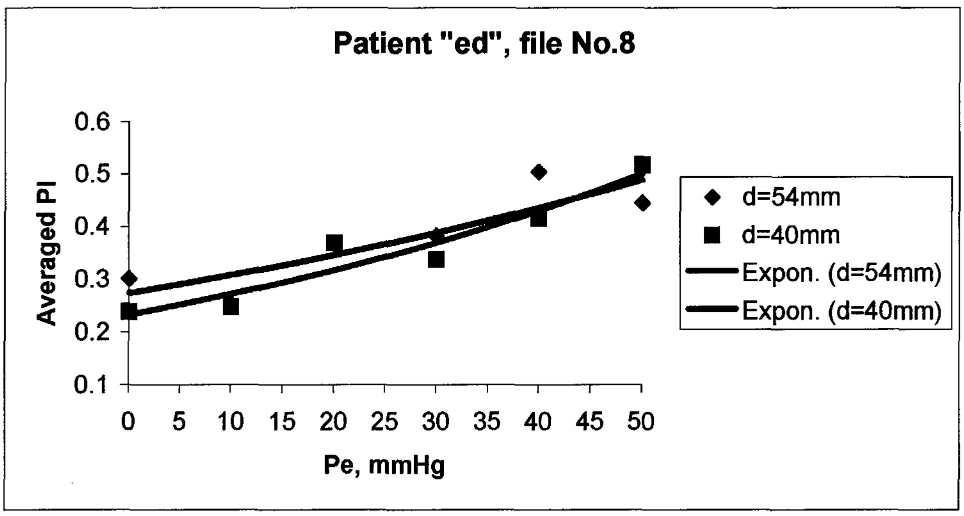
Trial No. 48 Invasive ICP=30mHg, non-invasive ICP=26mHg



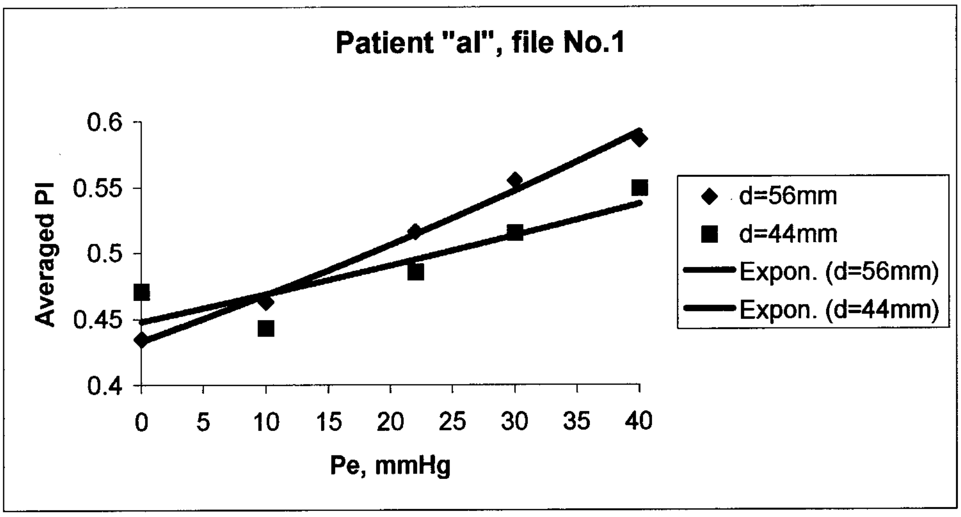
Trial No. 49 Invasive ICP=26mHg, non-invasive ICP=24mHg



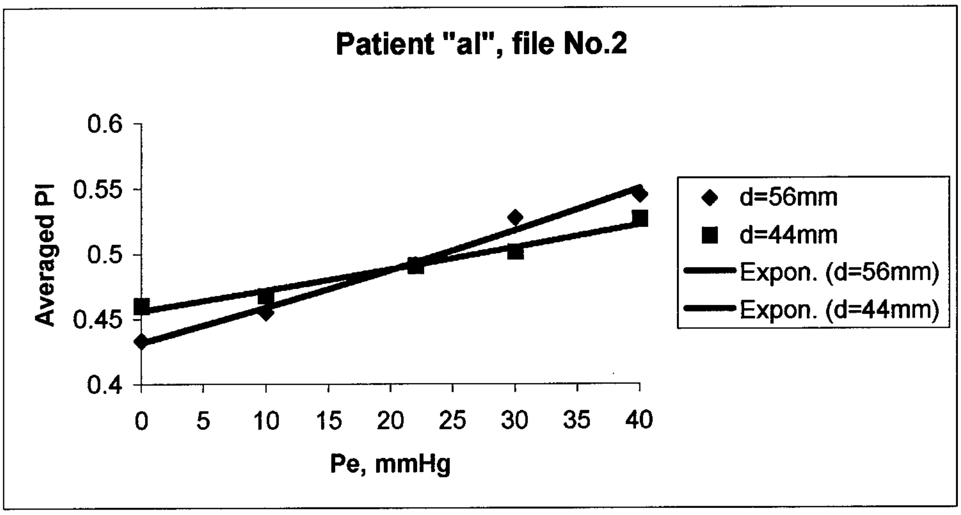
Trial No. 50 Invasive ICP=21mHg, non-invasive ICP=22mHg



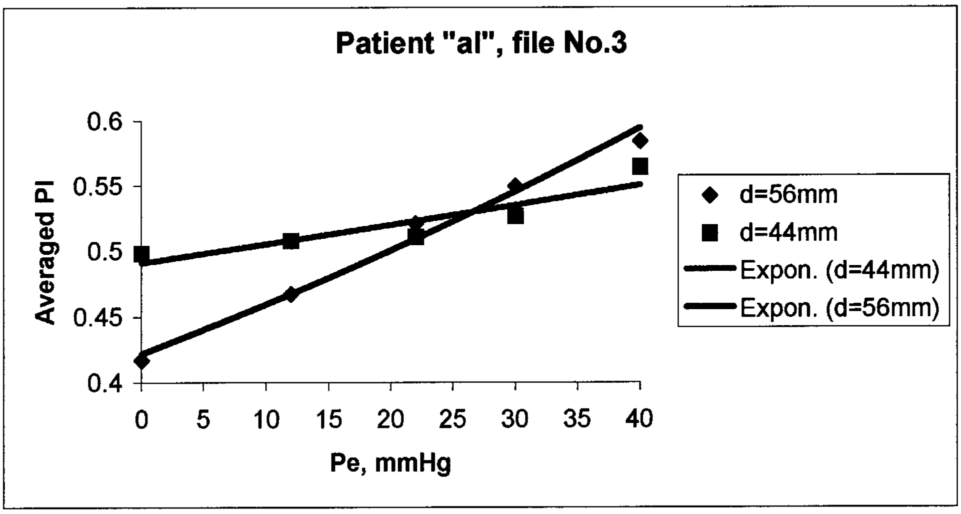
Trial No. 51 Invasive ICP=33mHg, non-invasive ICP=43mHg



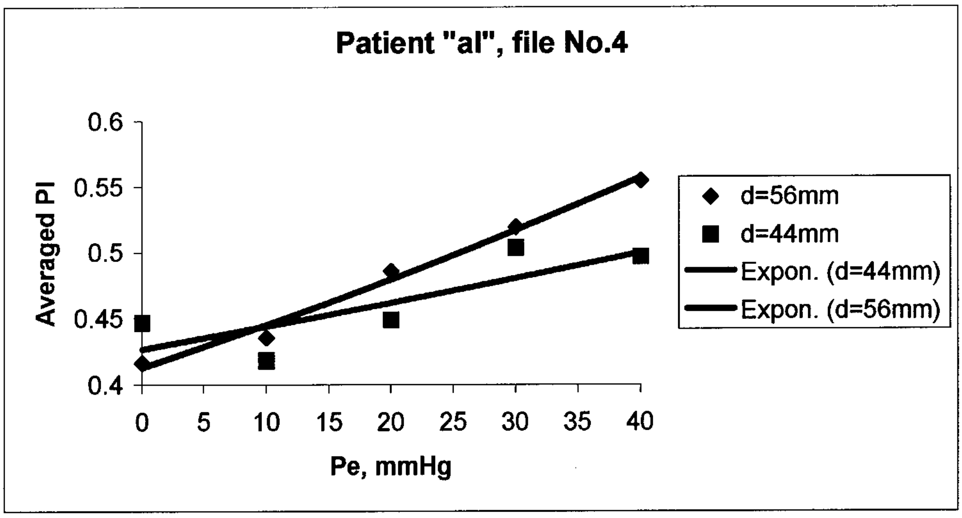
Trial No. 52 Invasive ICP=18mmHg, non-invasive ICP=10mmHg



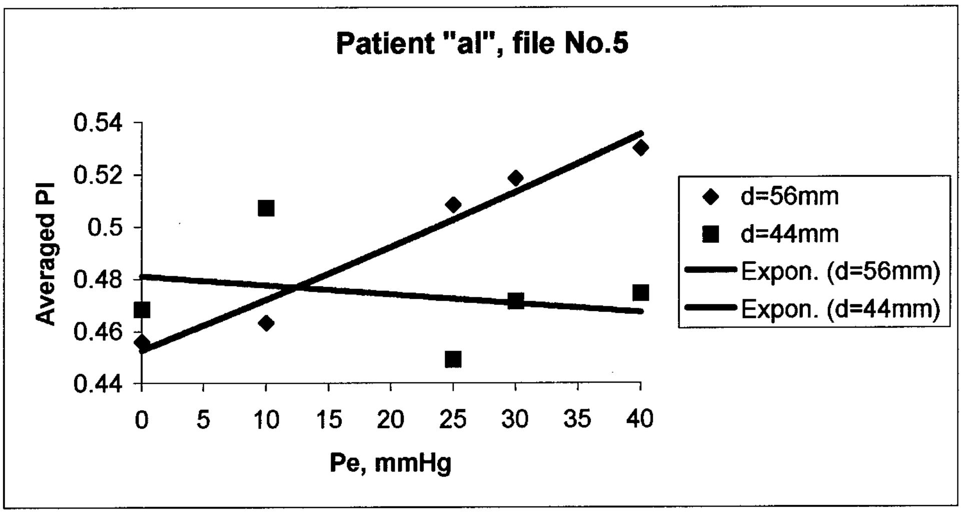
Trial No. 53 Invasive ICP=20mmHg, non-invasive ICP=20mmHg



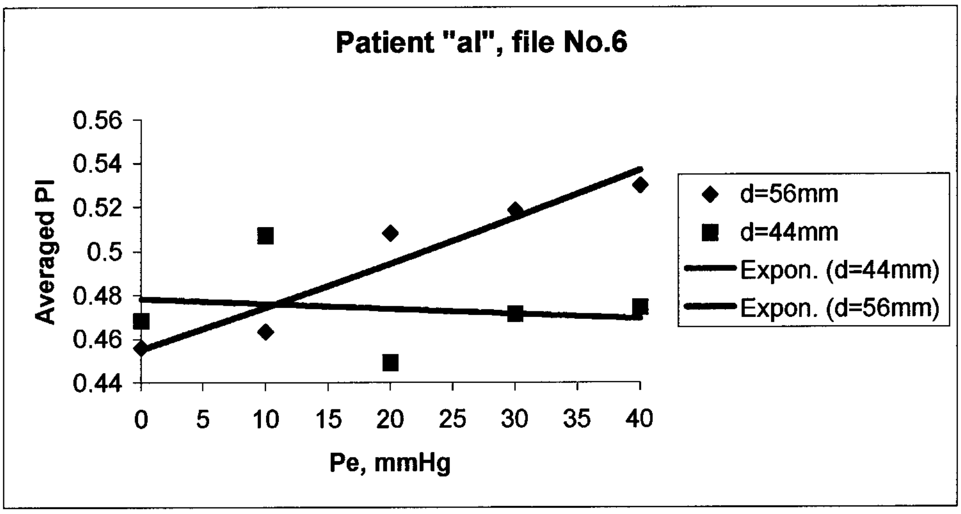
Trial No. 54 Invasive ICP=24mmHg, non-invasive ICP=26mHg



Trial No. 55 Invasive ICP=22mmHg, non-invasive ICP=10mHg



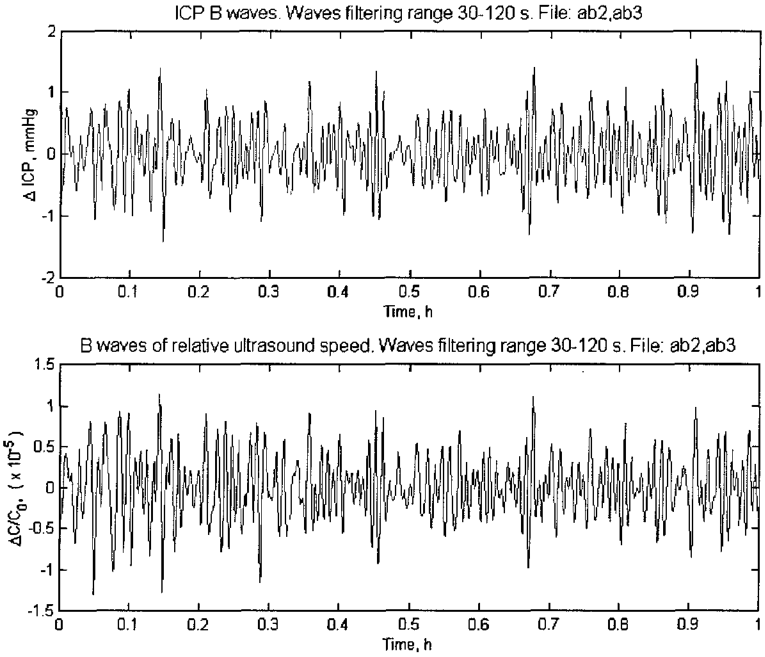
Trial No. 56 Invasive ICP=19mmHg, non-invasive ICP=13mHg



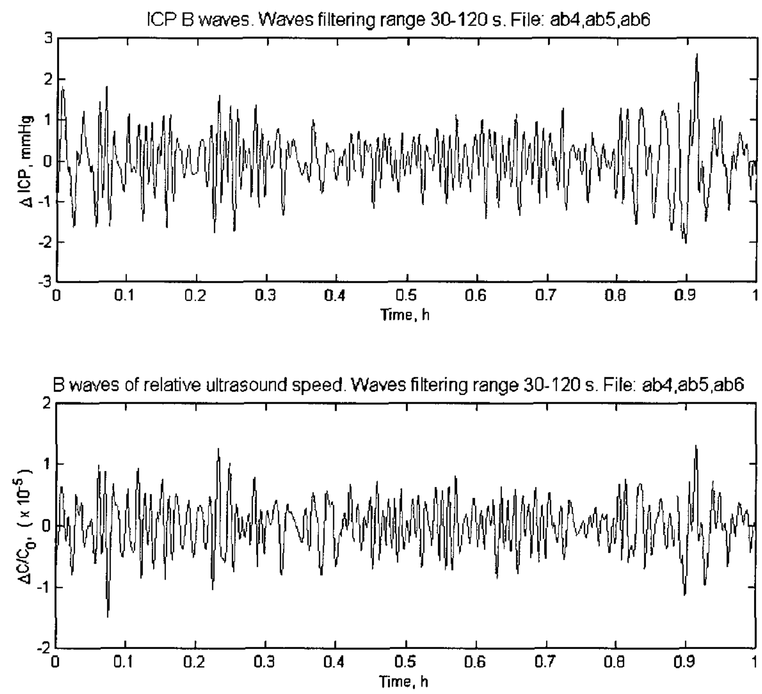
Trial No. 57 Invasive ICP=16mmHg, non-invasive ICP=12mHg

APPENDIX B

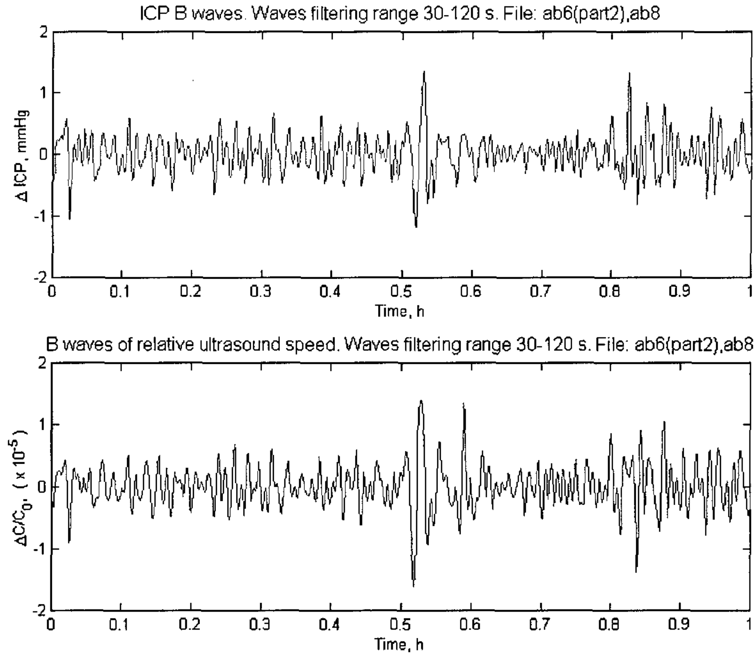
CLINICAL RESULTS OF SIMULTANEOUS INVASIVE SLOW INTRACRANIAL PRESSURE AND NON-INVASIVE SLOW INTRACRANIAL BLOOD VOLUME WAVES MEASUREMENT



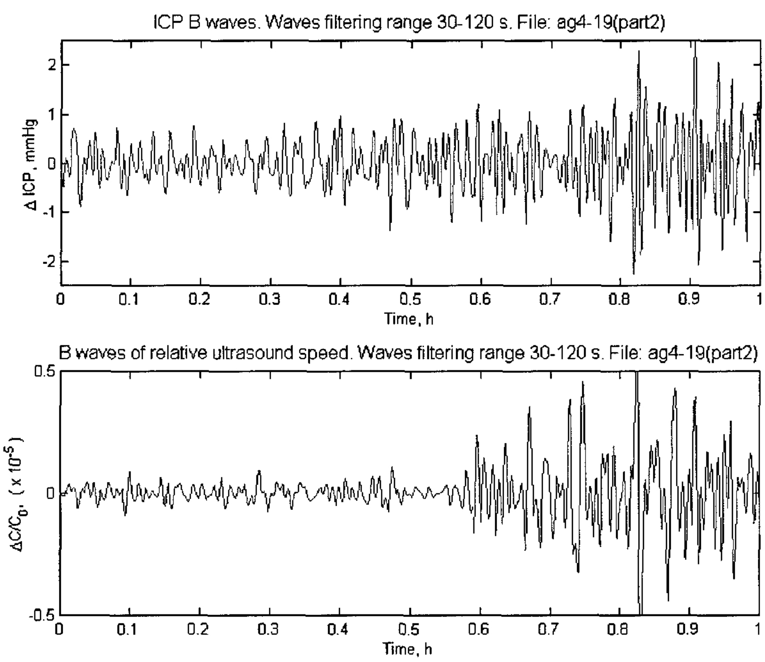
File: ab2&ab3. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.9194



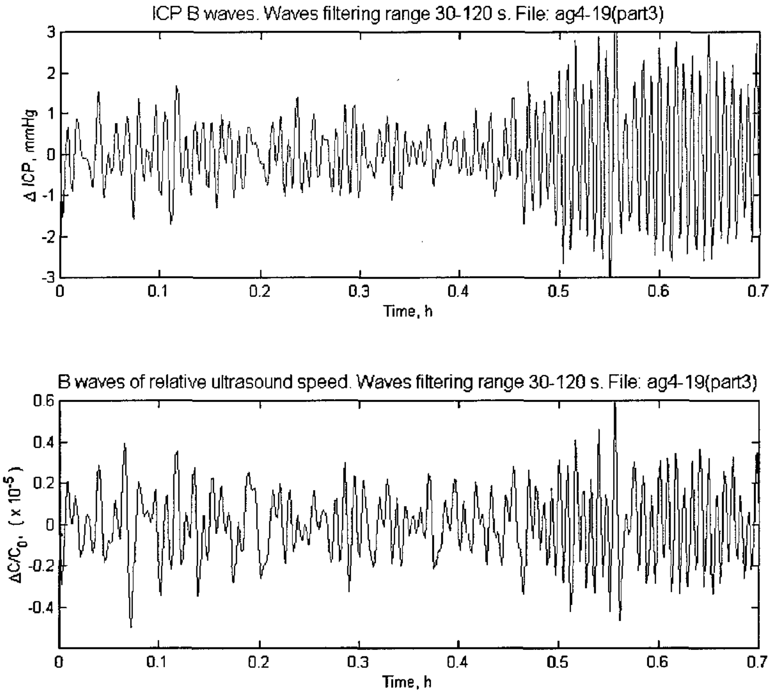
File:ab4&5&6. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.8313



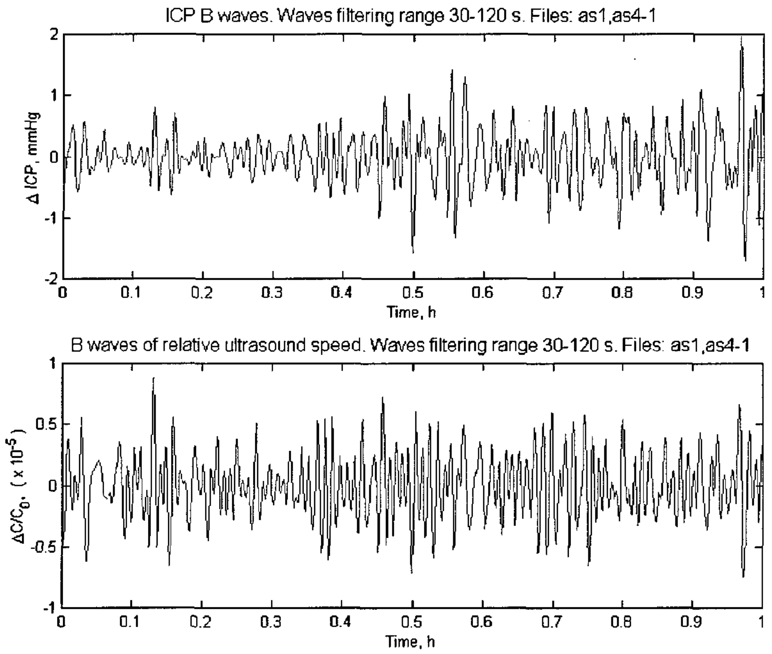
File: ab6-part2&ab8. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.7803



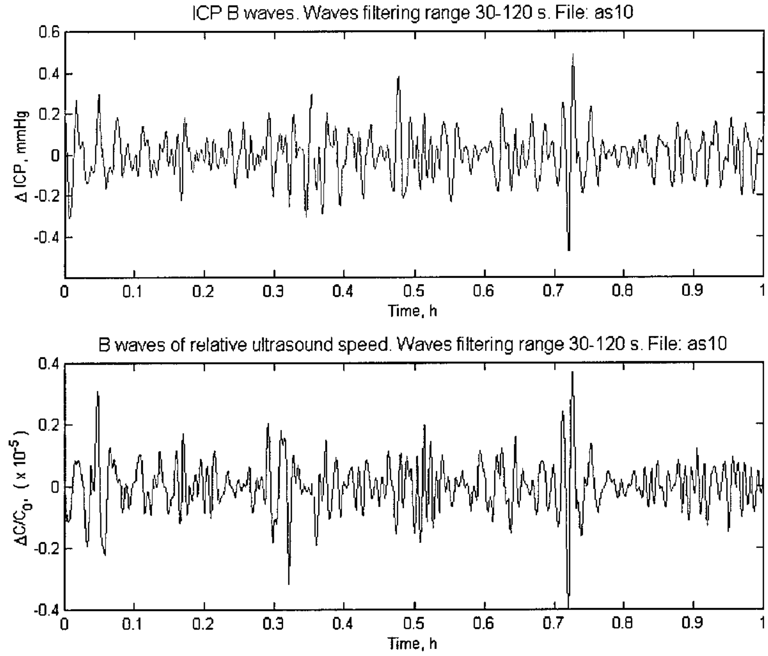
File: ag4_19part2. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.5780



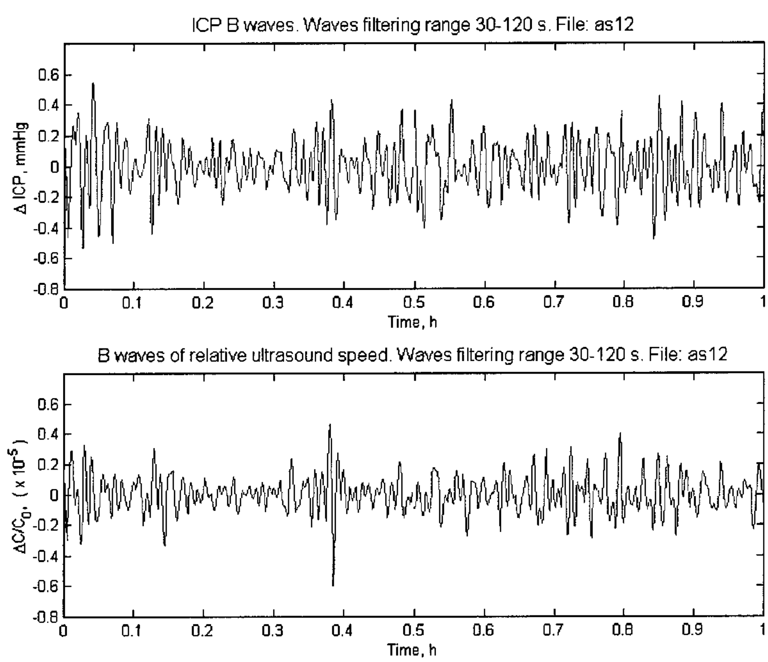
File:ag4_19part3. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.6457



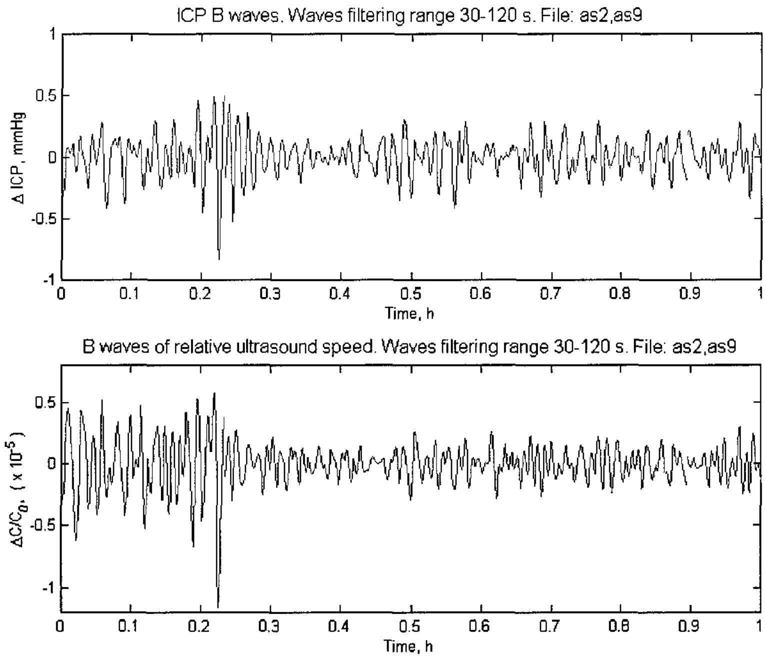
File: as1&as4. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.6380



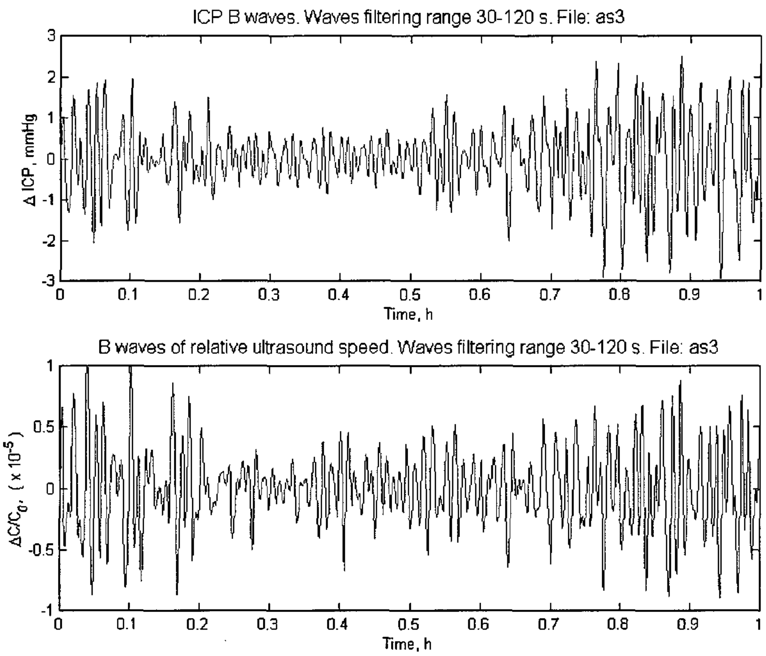
File: as10. Correlation coefficient r(ICP, $\Delta C/C_0$)= 0.5701



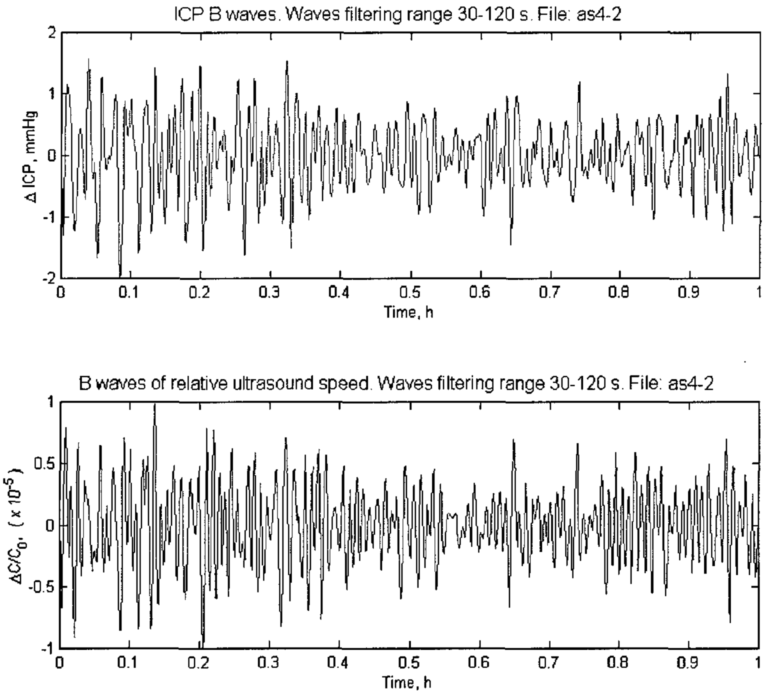
File: as12. Correlation coefficient r(ICP, $\Delta C/C_0$)= 0.4421



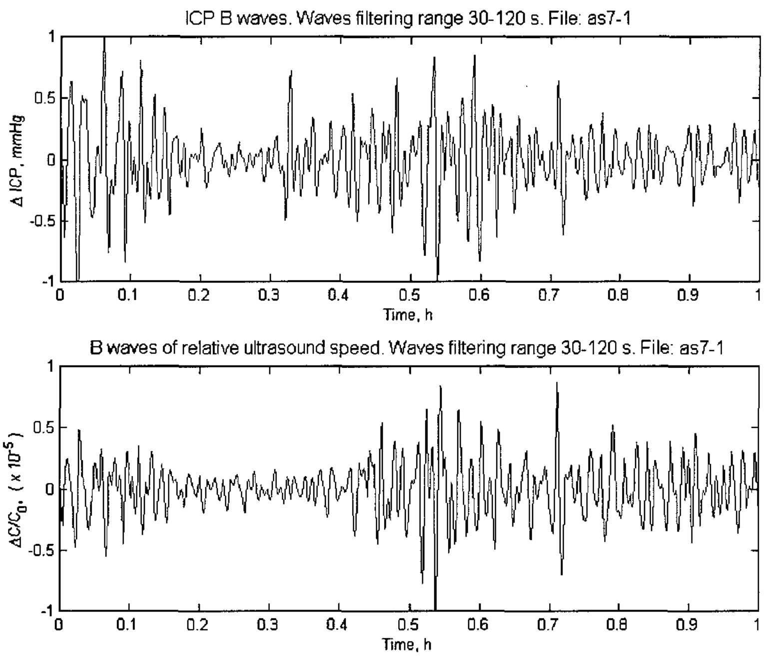
File:as2&as9. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.6560



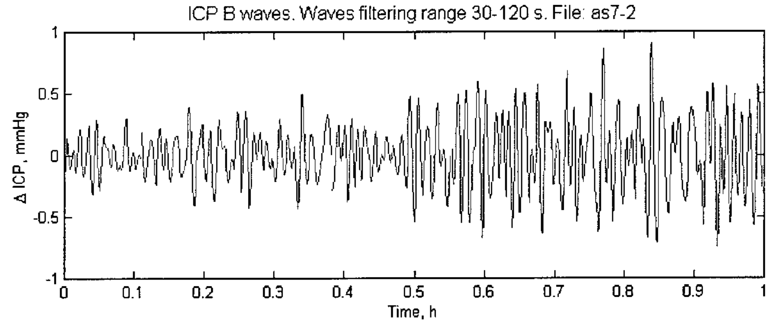
File: as3. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.7976

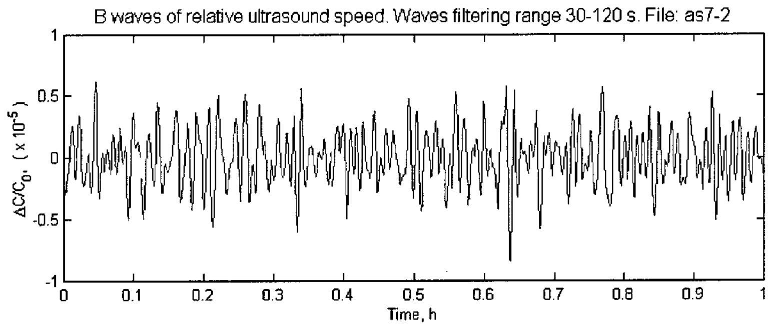


File: as4-2. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.6748

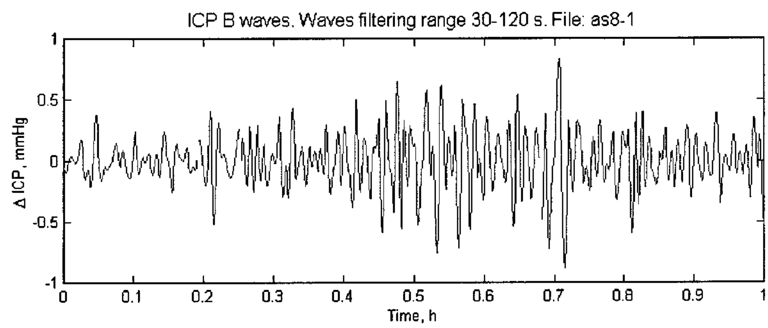


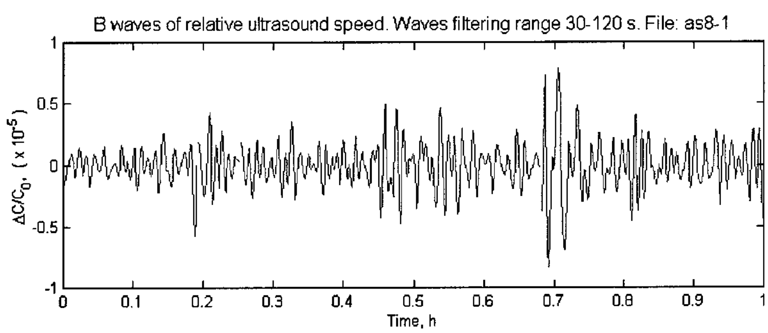
File: as7-1. Correlation coefficient r(ICP, $\Delta C/C_0$)= 0.5193



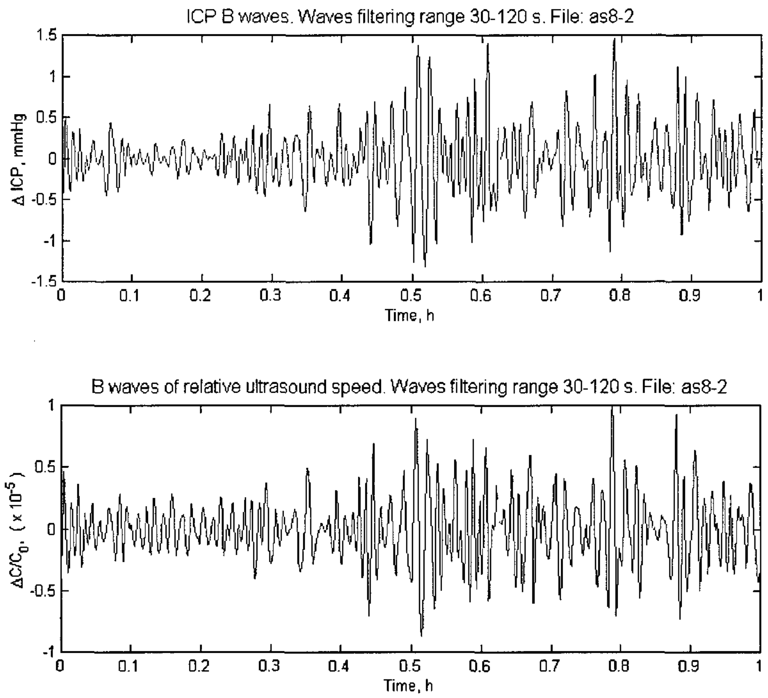


File: as7-2. Correlation coefficient r(ICP, $\Delta C/C_0$)= 0.4548

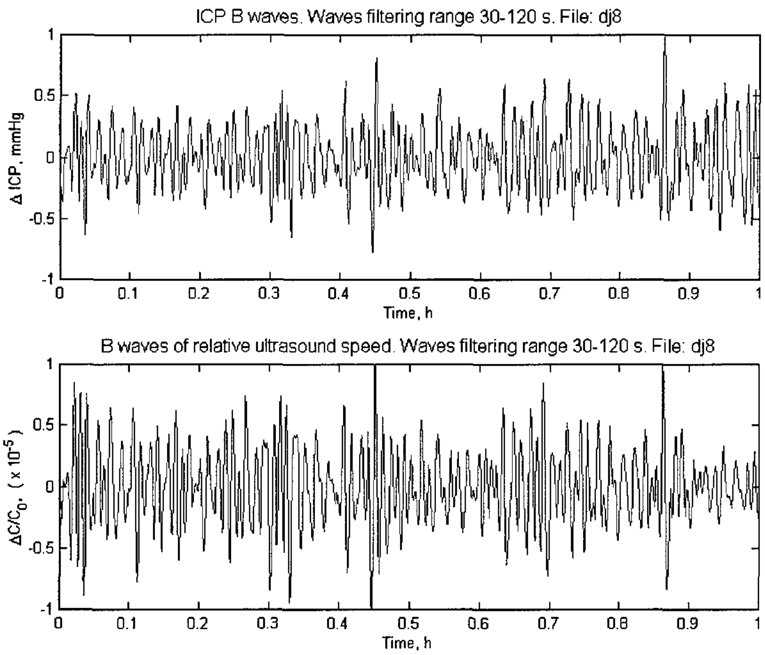




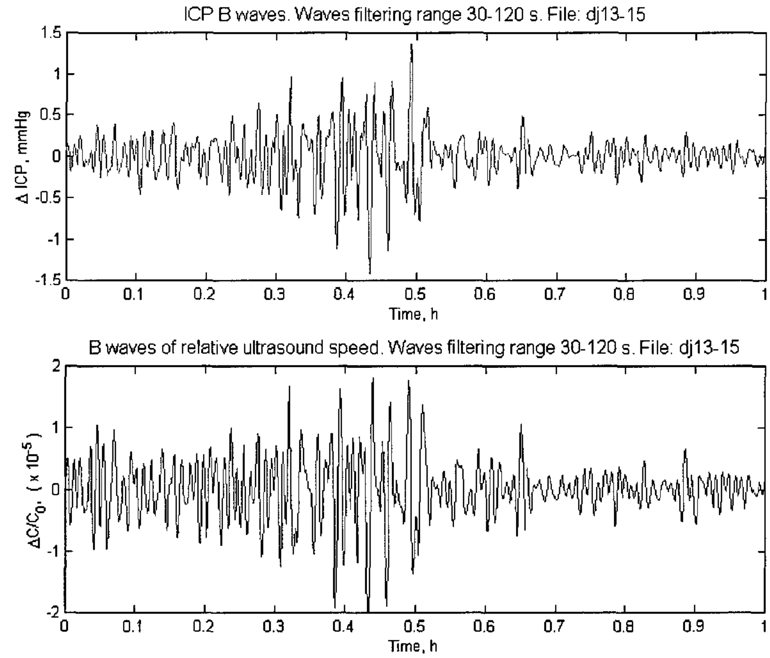
File: as8-1. Correlation coefficient r(ICP, $\Delta C/C_0$)= 0.7578



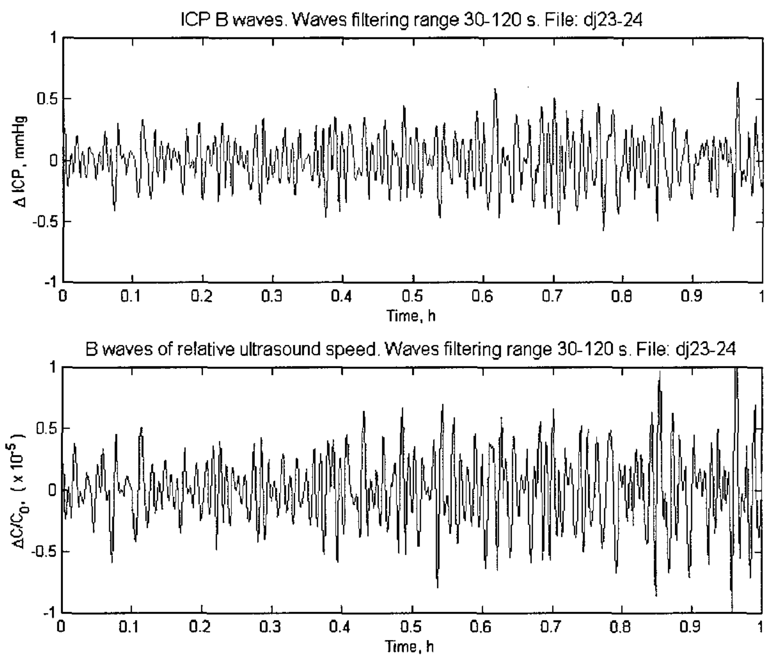
File: as8-2. Correlation coefficient r(ICP, $\Delta C/C_0$)= 0.7294



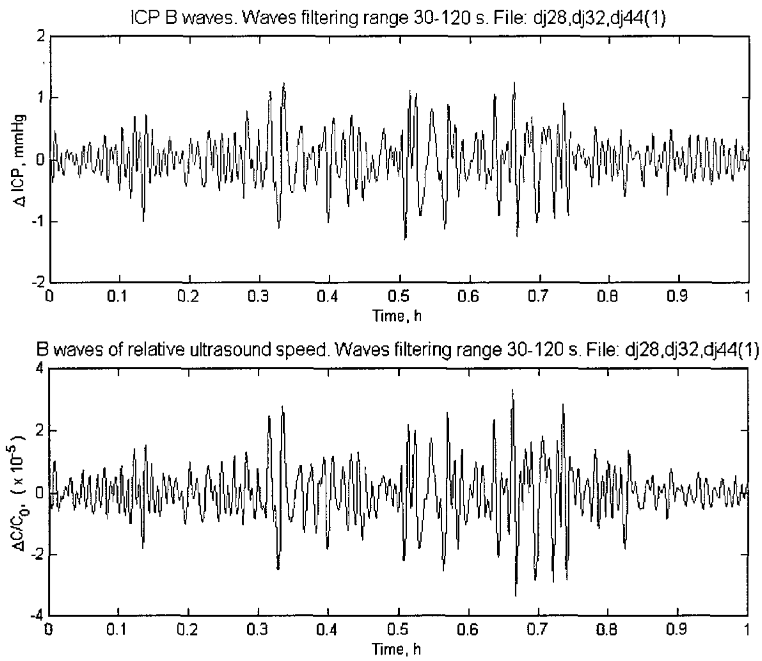
File: dj8. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.8704



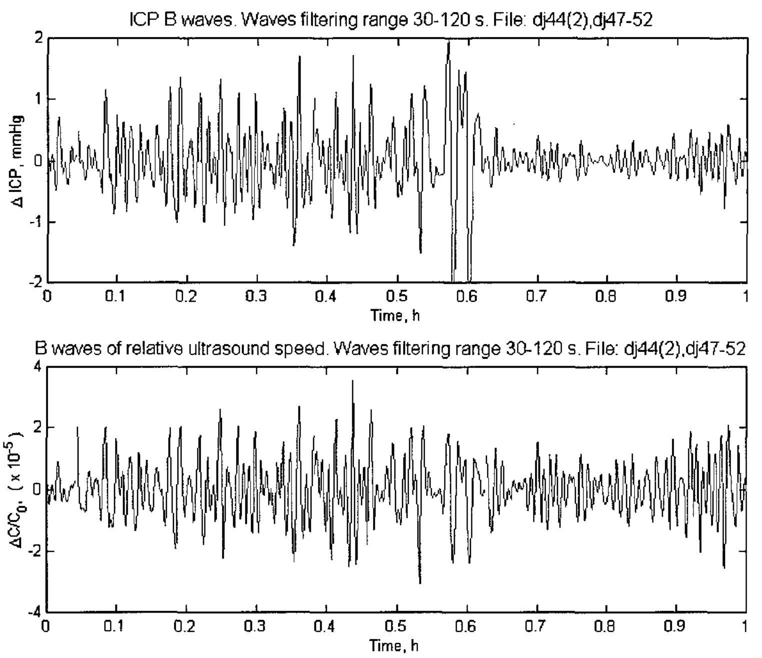
File: dj13_15. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.8585



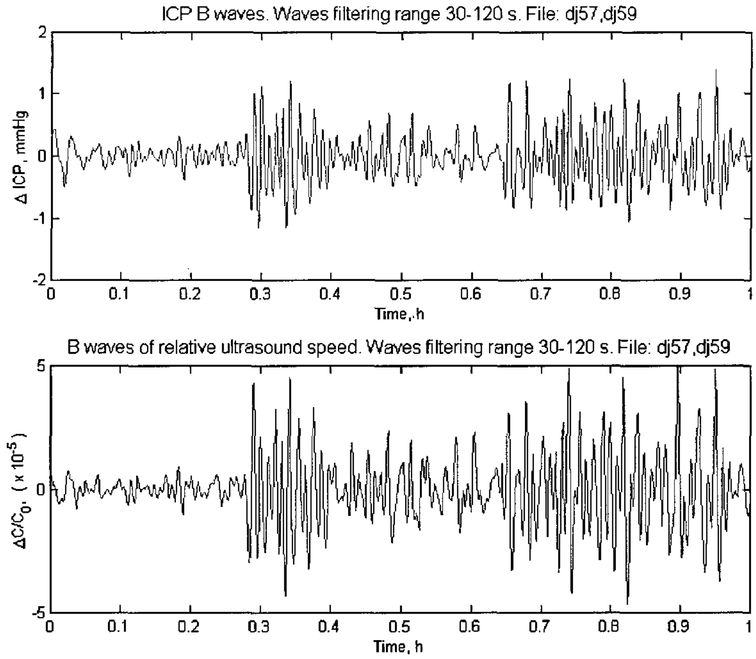
File: dj23_24. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.8002



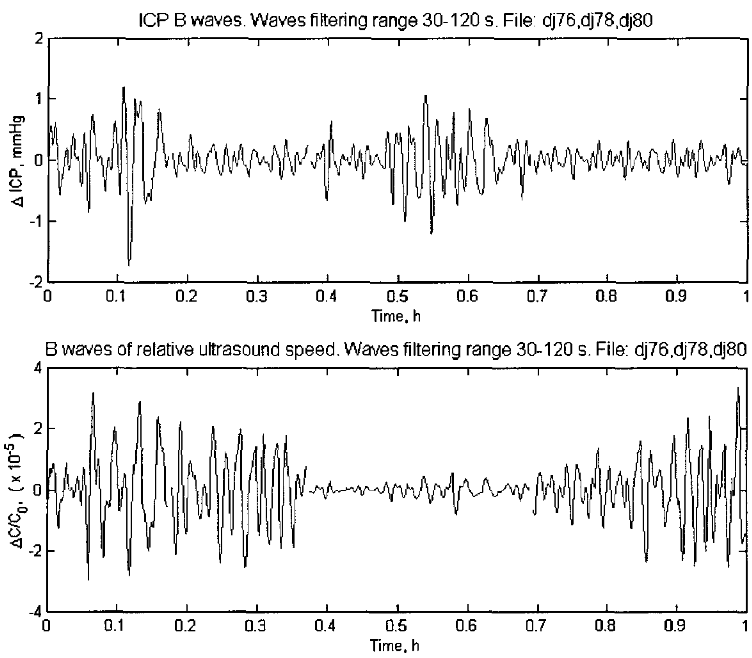
File: dj28_32&dj44part1. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.9335



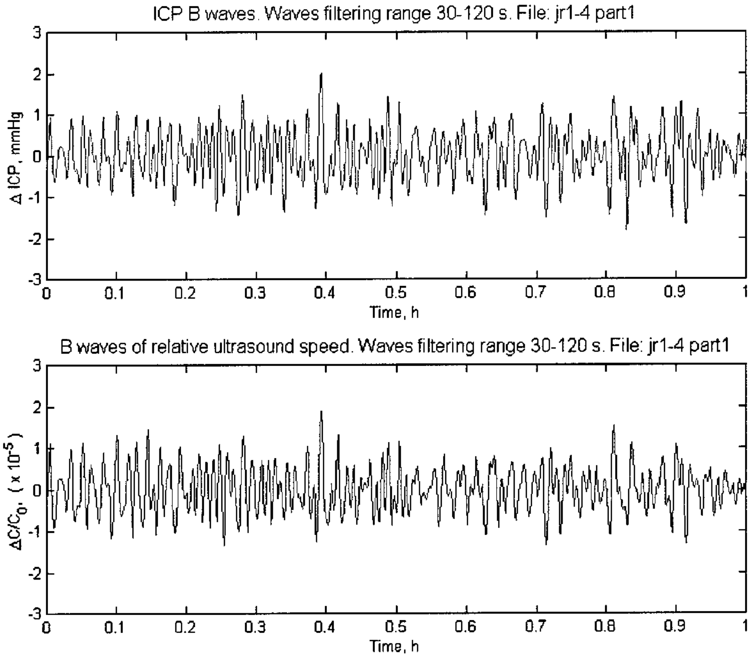
File: dj44part2&dj47_52. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.7978



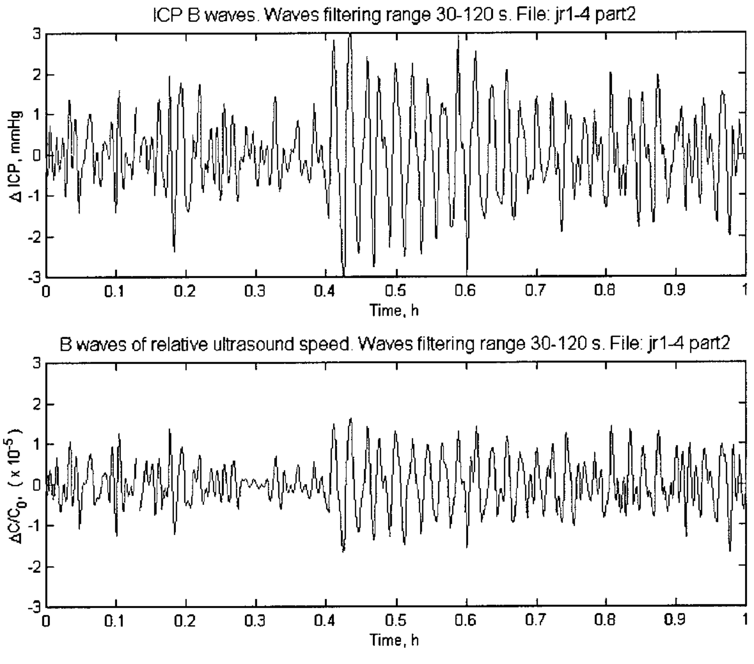
File: dj57&dj59. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.9276



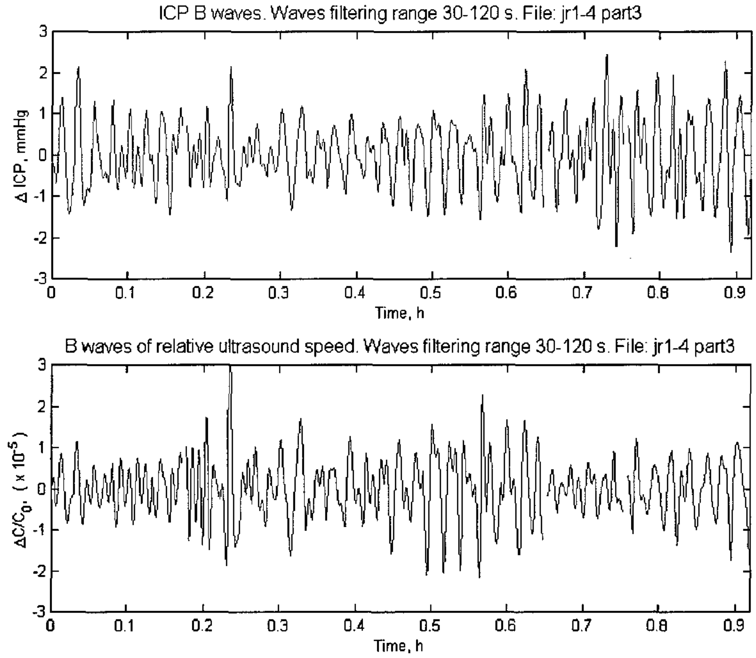
File: dj76-80. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.5059



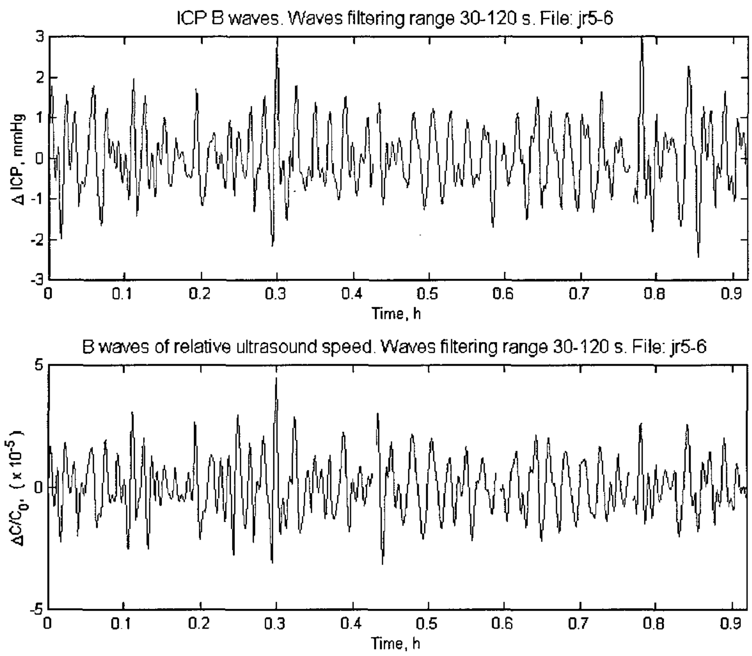
File: jr1-4_part1. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.8856



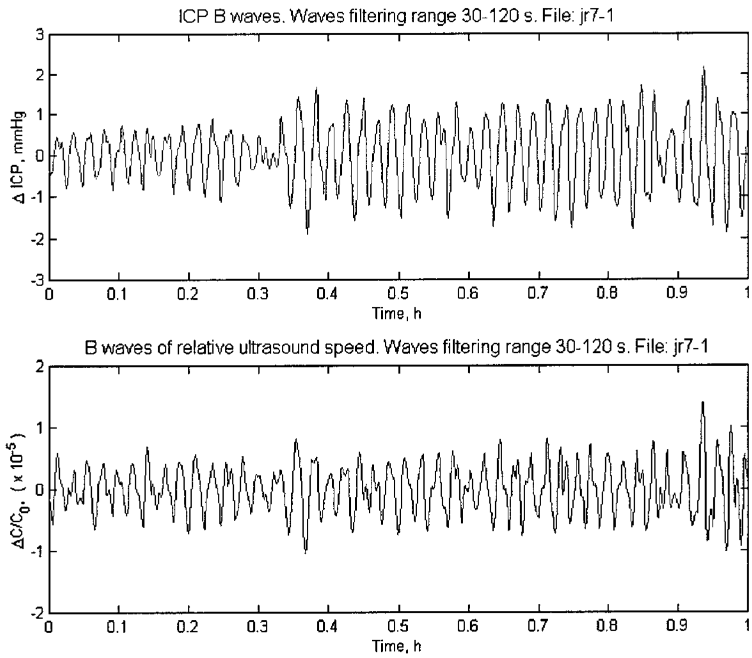
File: jr1-4_part2. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.9100



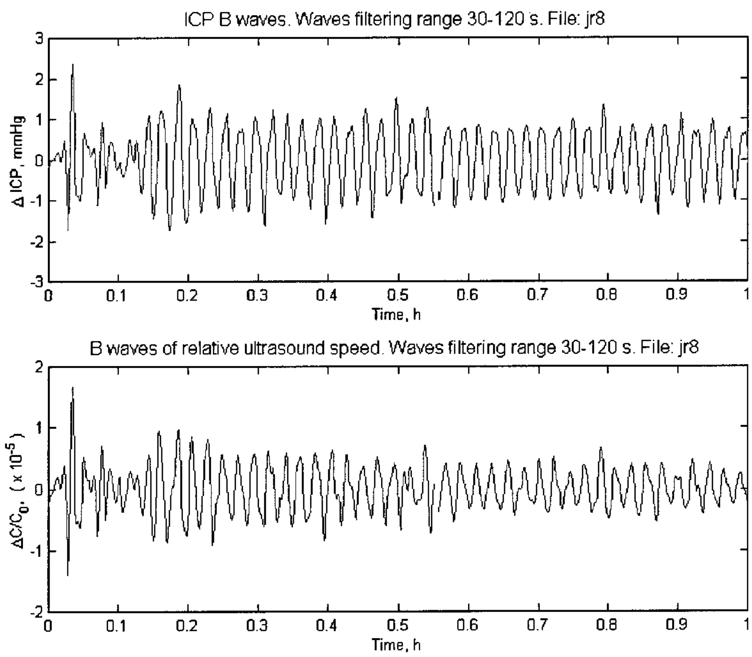
File: jr1-4_part3. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.7521



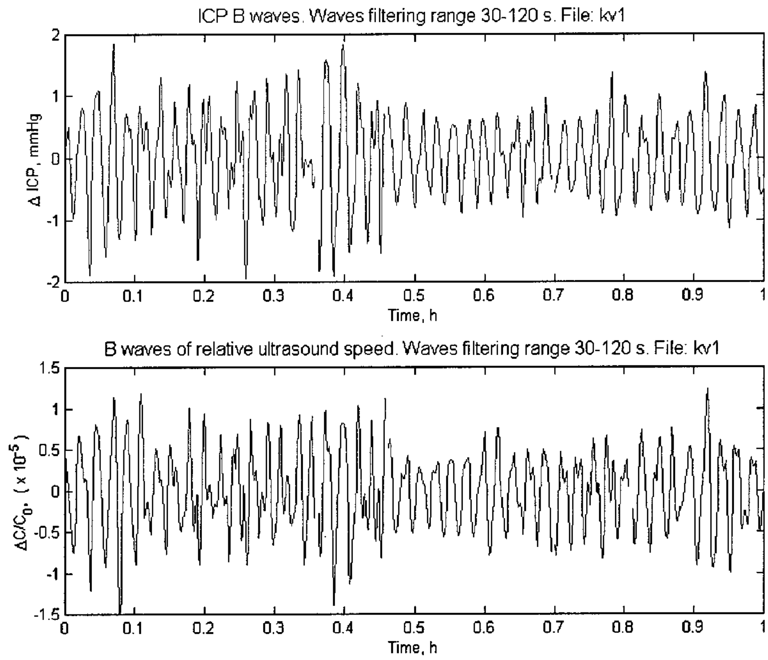
File: jr5-6. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.8373



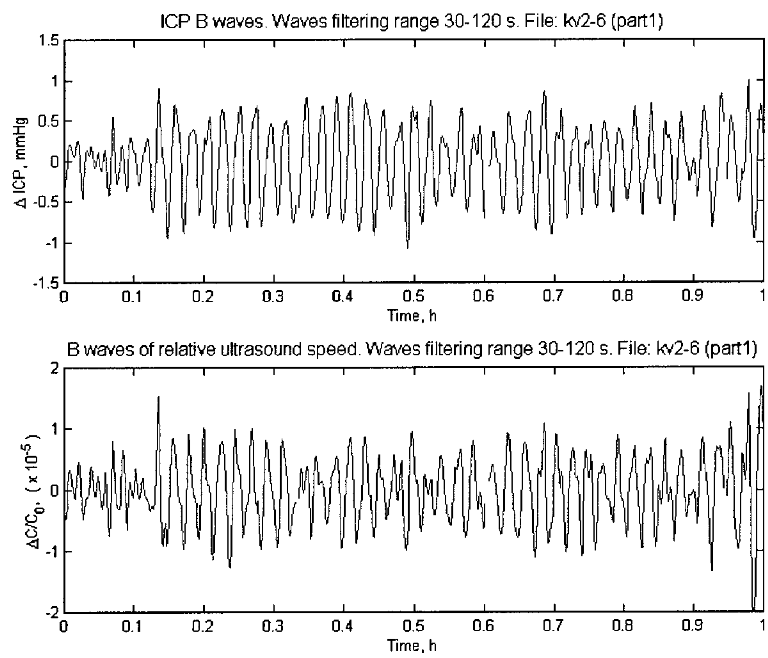
File: jr7part1. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.6519



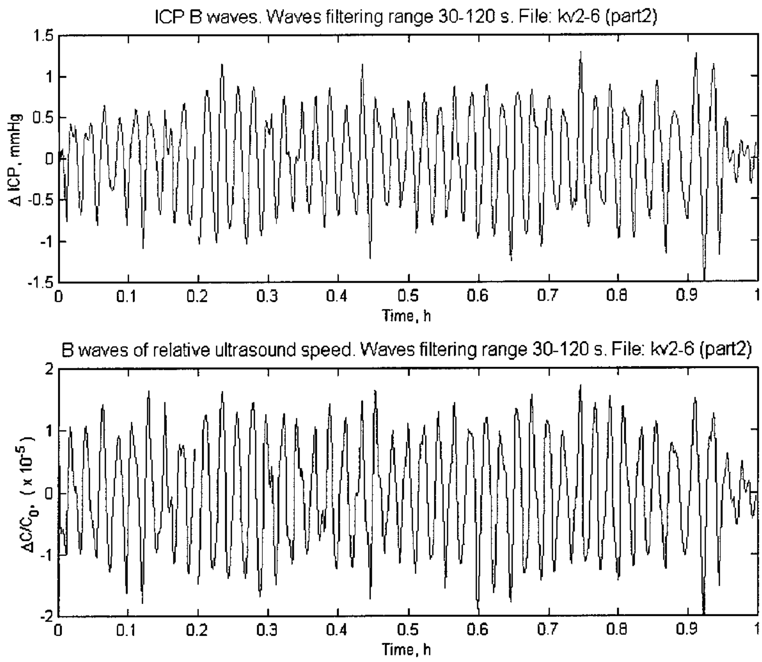
File: jr8. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.6549



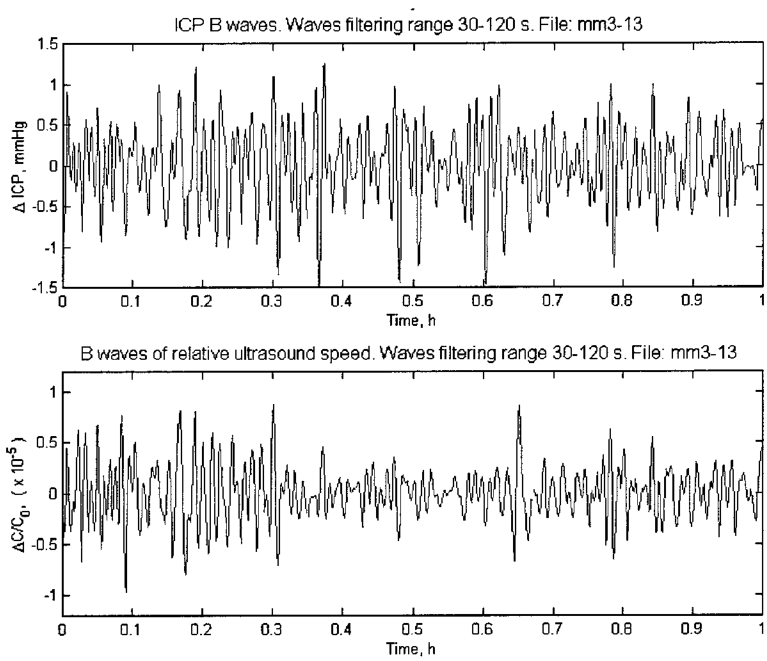
File: kv1. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.7374



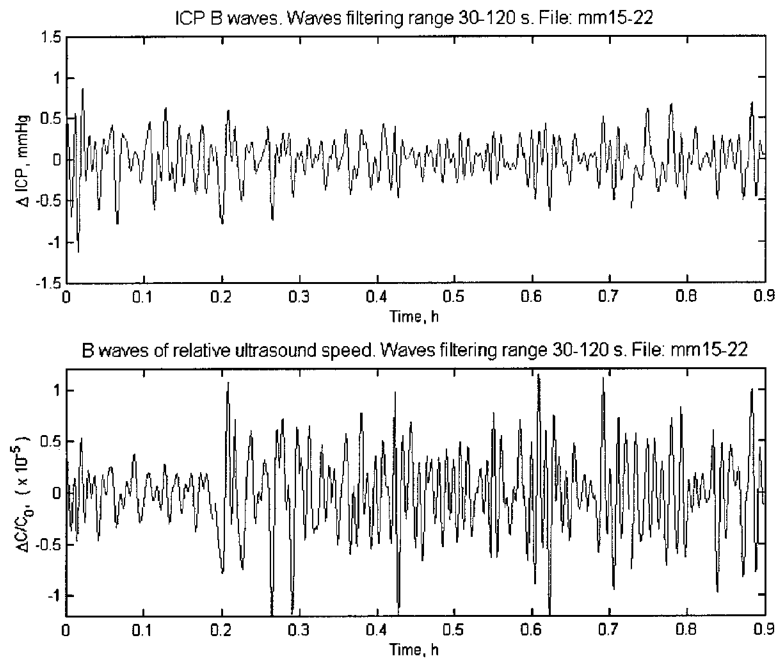
File: kv2_6part1. Correlation coefficient r(ICP, $\Delta C/C_0$) = 7343



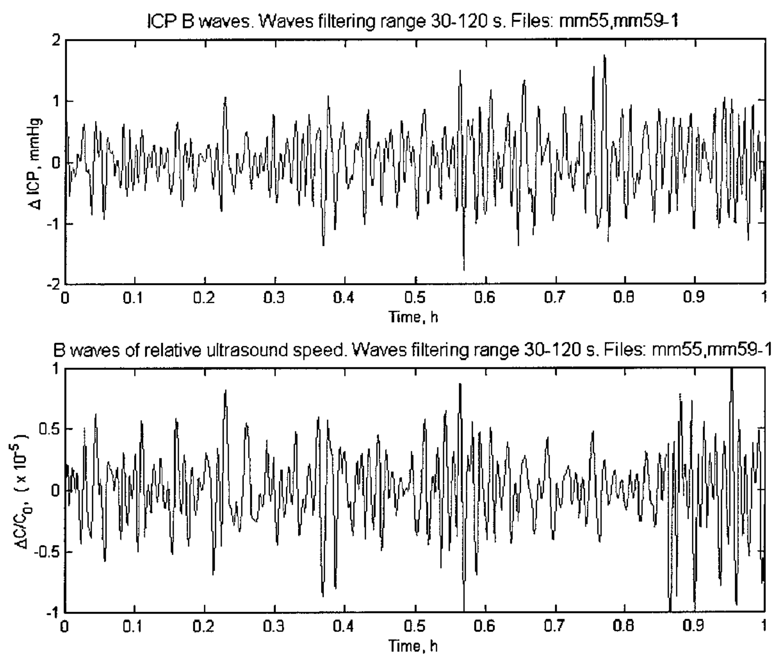
File: kv2_6part2. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.8761



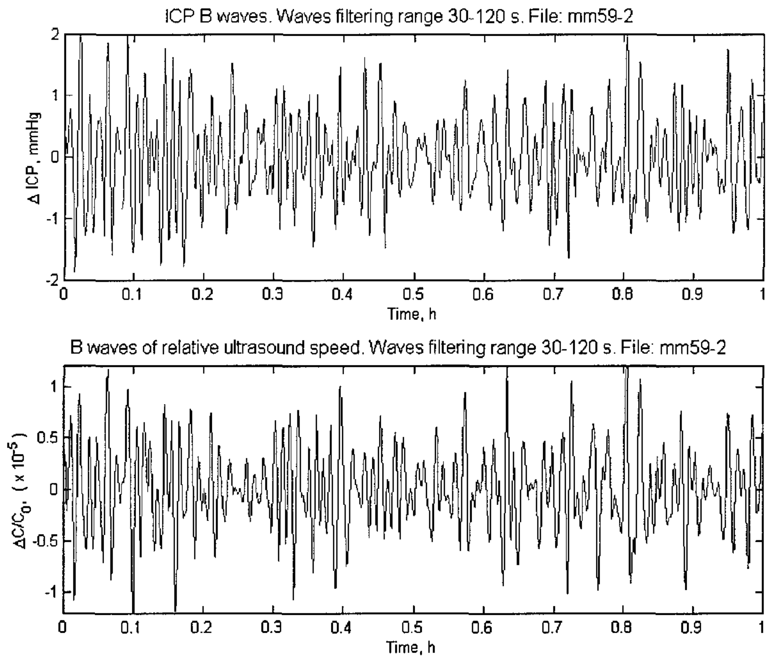
File: mm3_13part1. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.7489



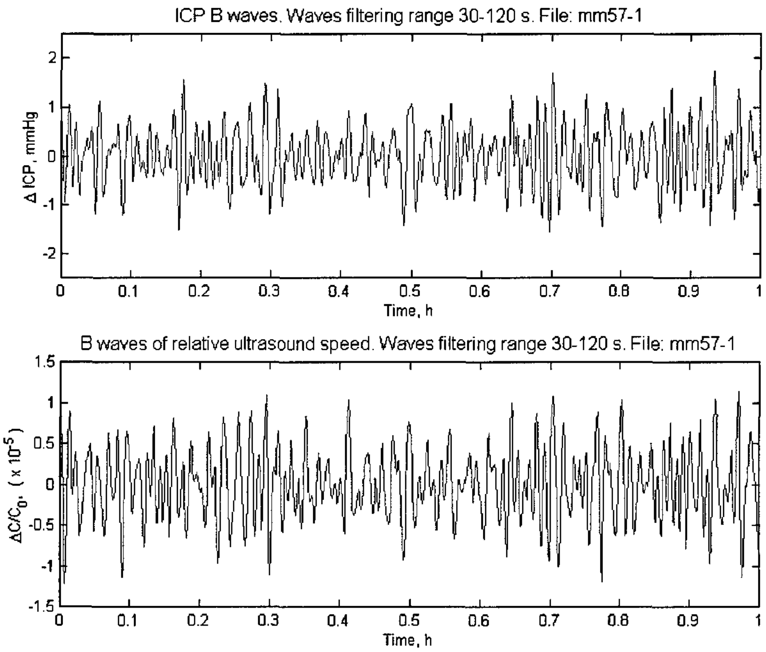
File: mm15_22. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.7566



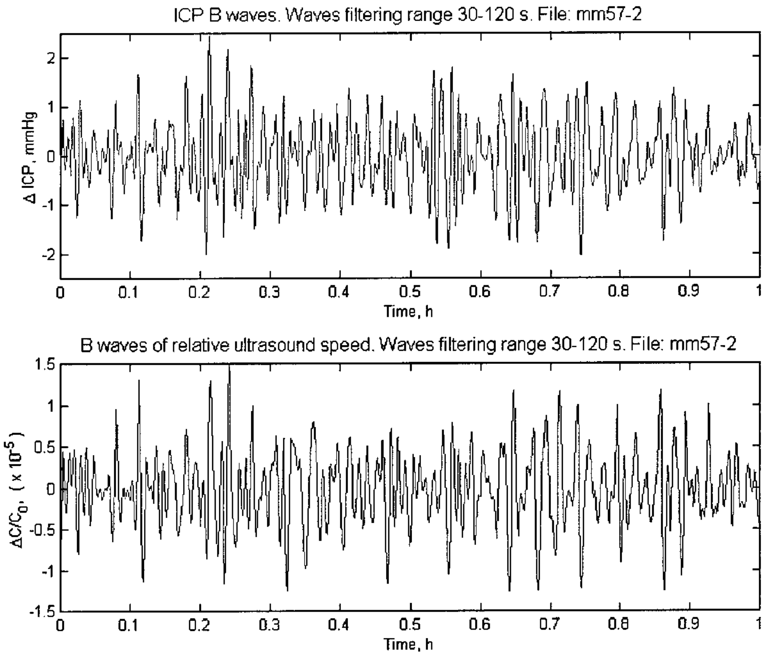
File: mm55&mm59_1. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.6674



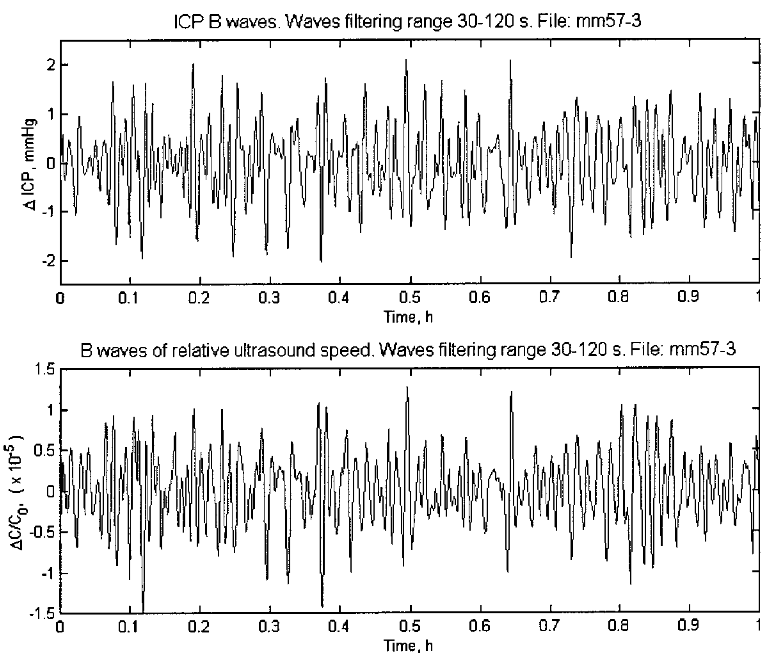
File: mm59_2. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.7088



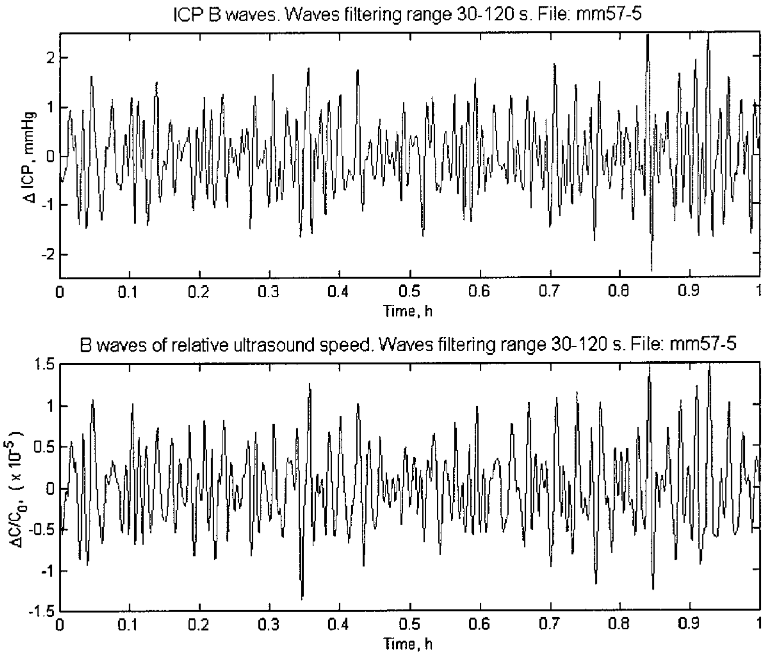
File: mm57_1. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.5706



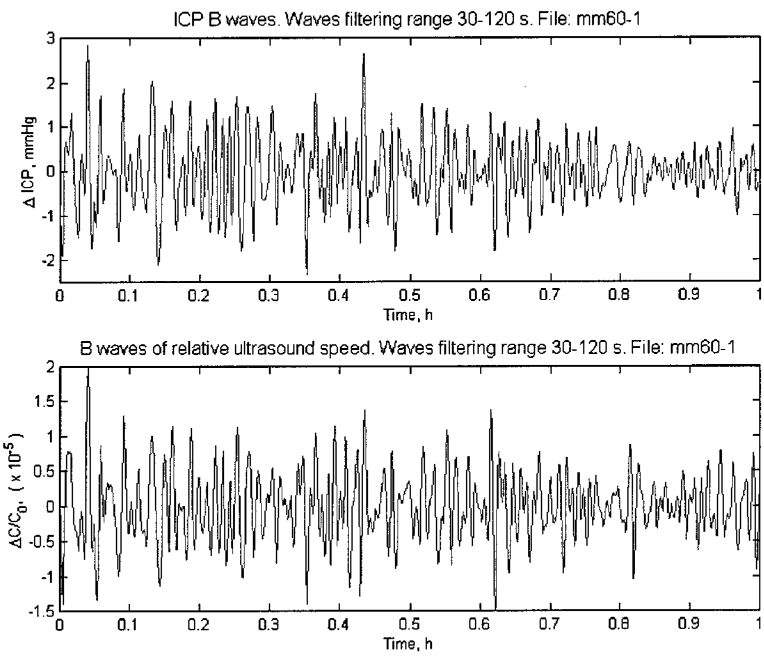
File: mm57_2. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.6351



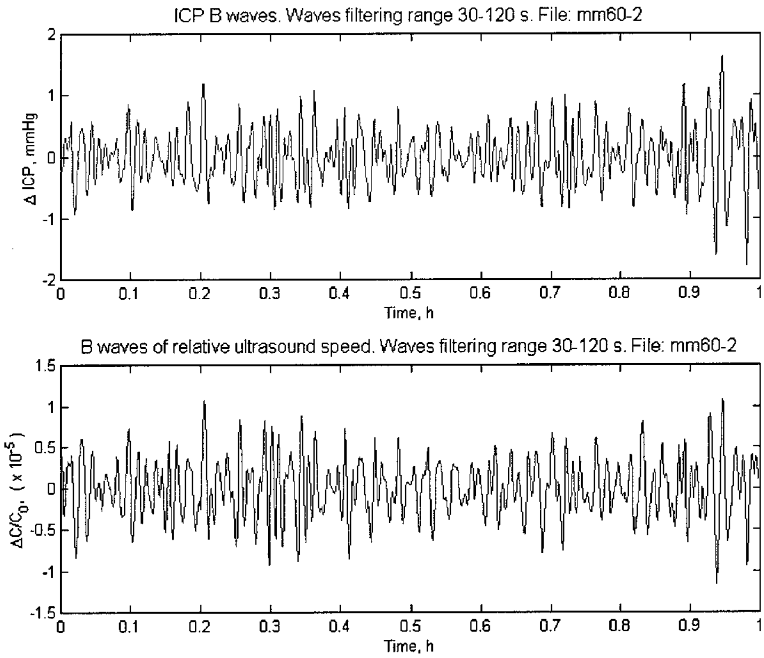
File: mm57_3. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.6869



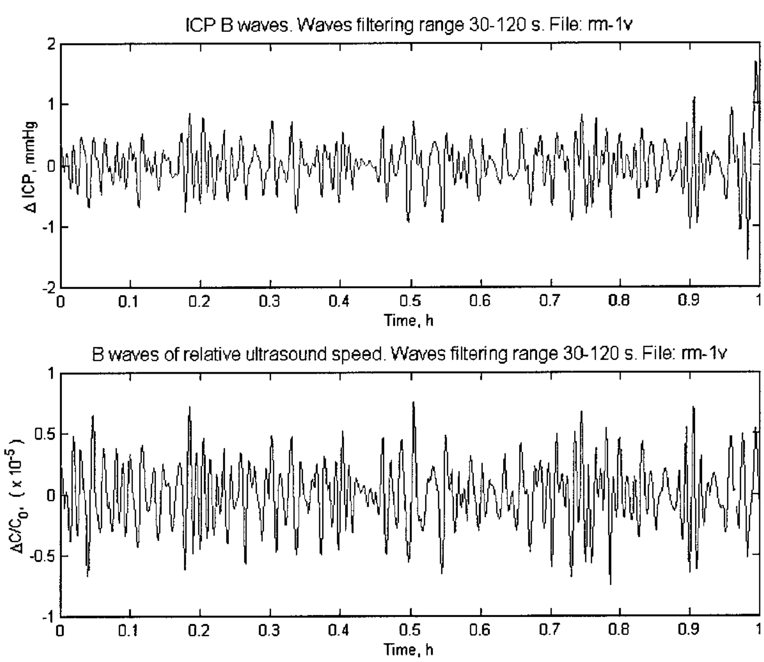
File: mm57_5. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.6019



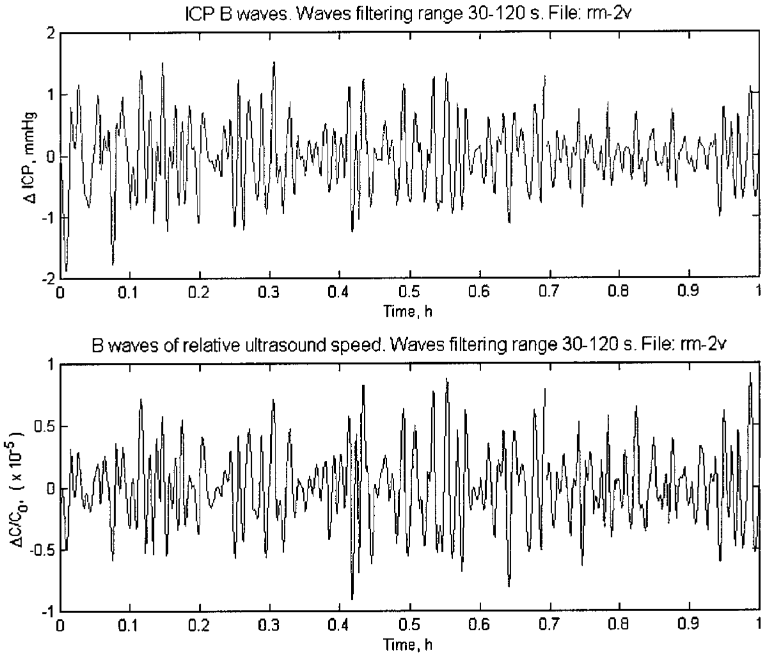
File: mm60_1. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.7361



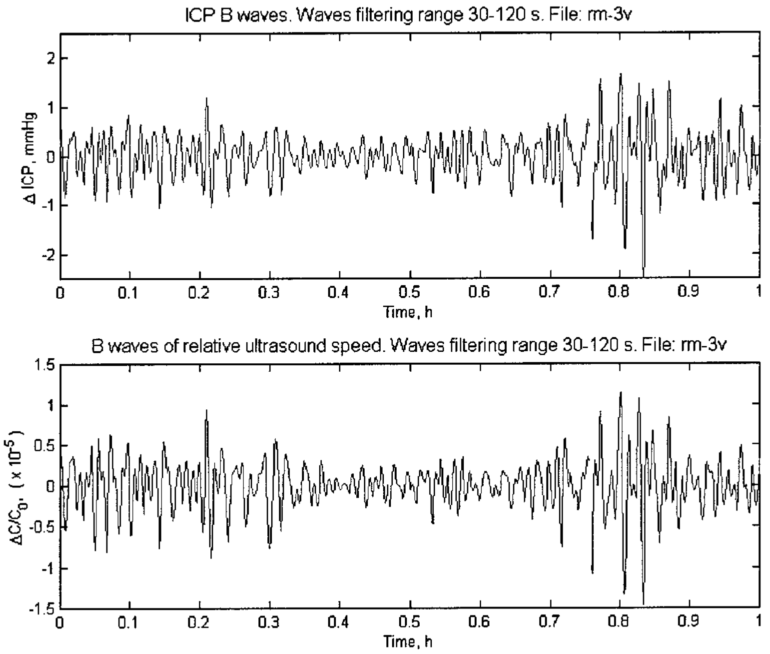
File: mm60_2. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.7307



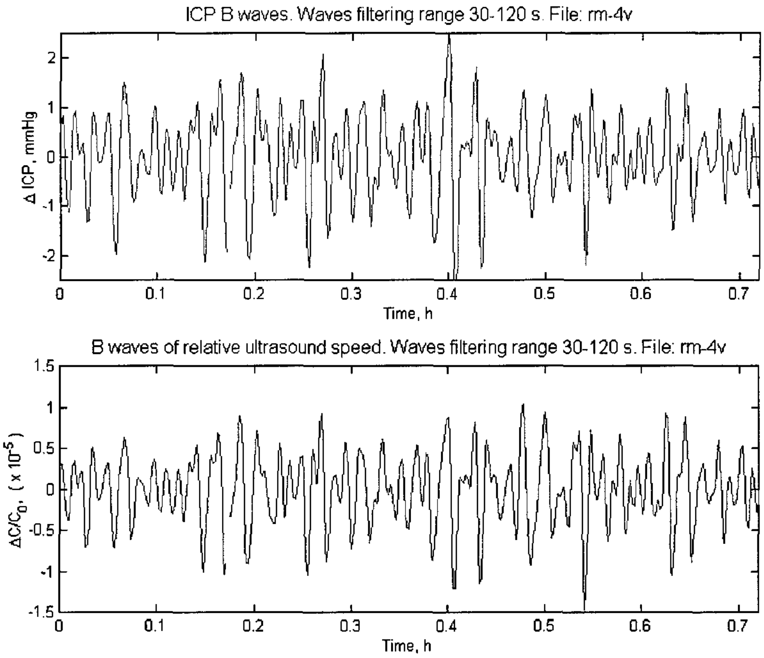
File: rm_1v. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.8695



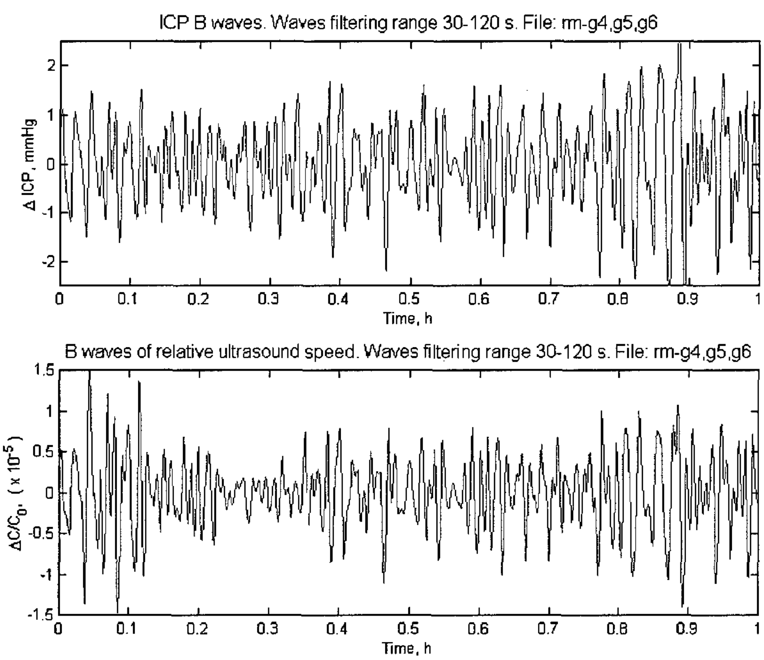
File: rm_2v. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.8989



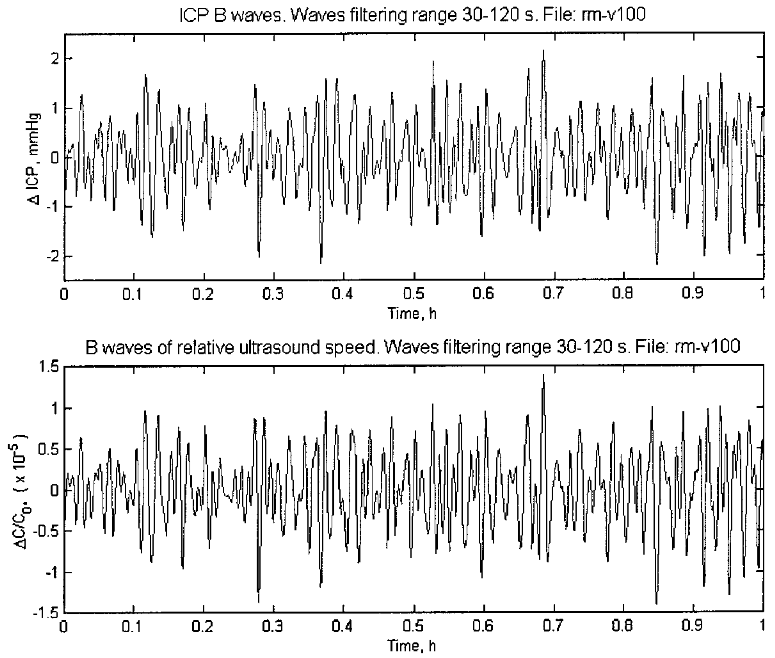
File: rm_3v. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.9339



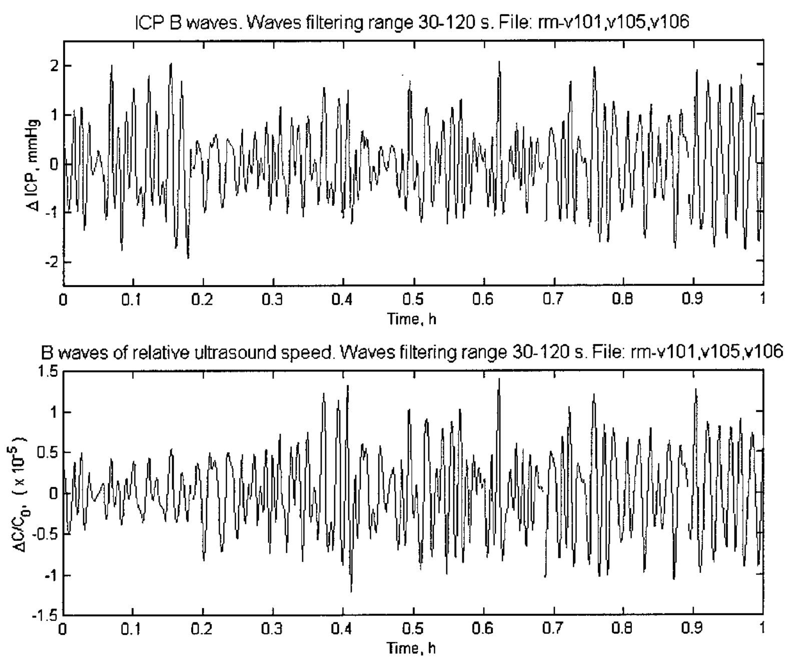
File: rm_4v. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.9612



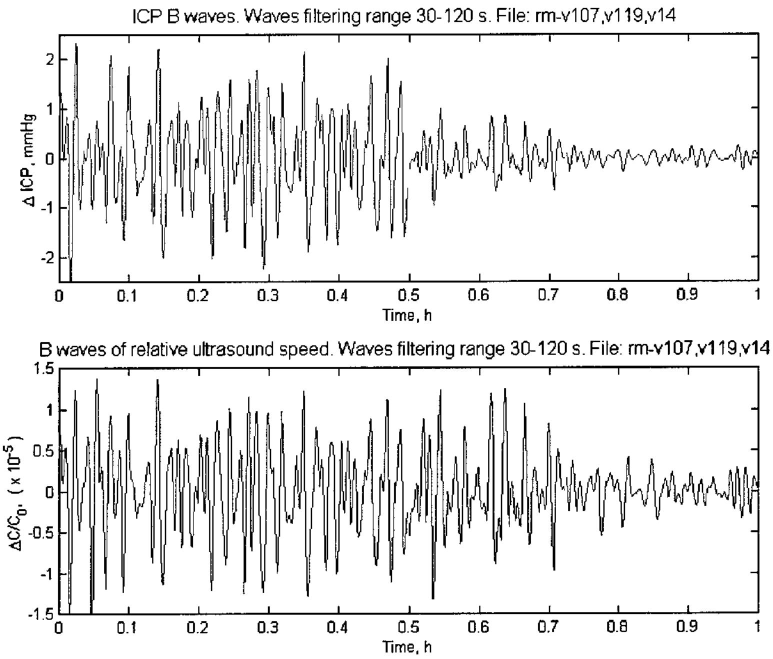
File: rm_g4g5g6. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.8875



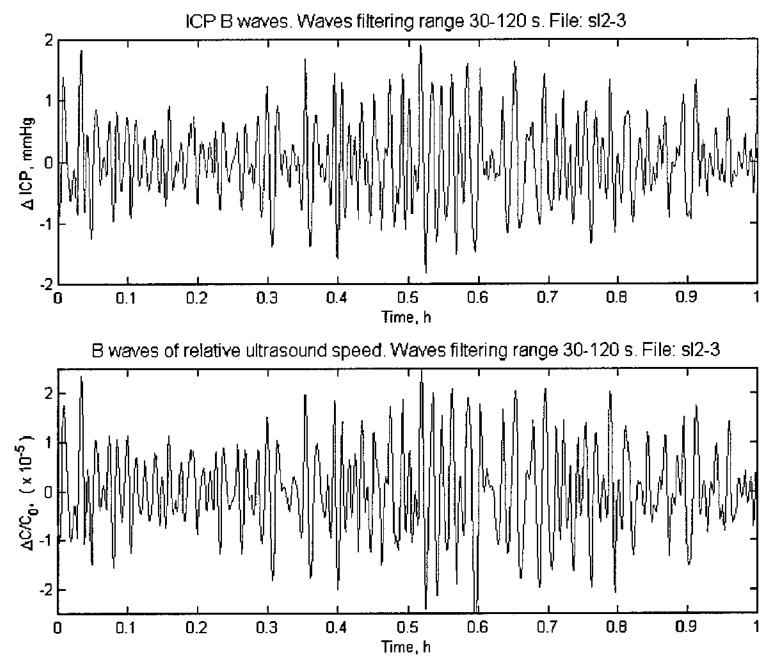
File: rm-v100. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.9788



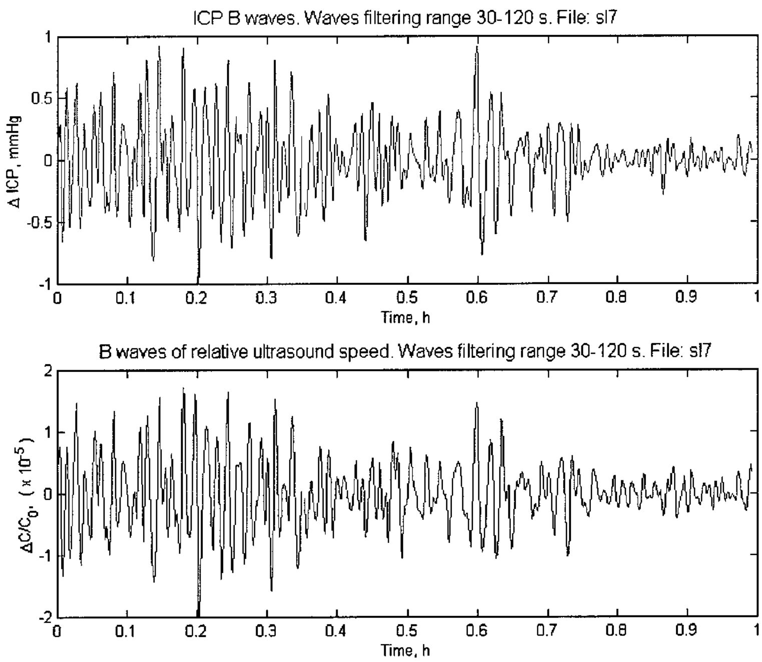
File: rm-101&v105&v106. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.9042



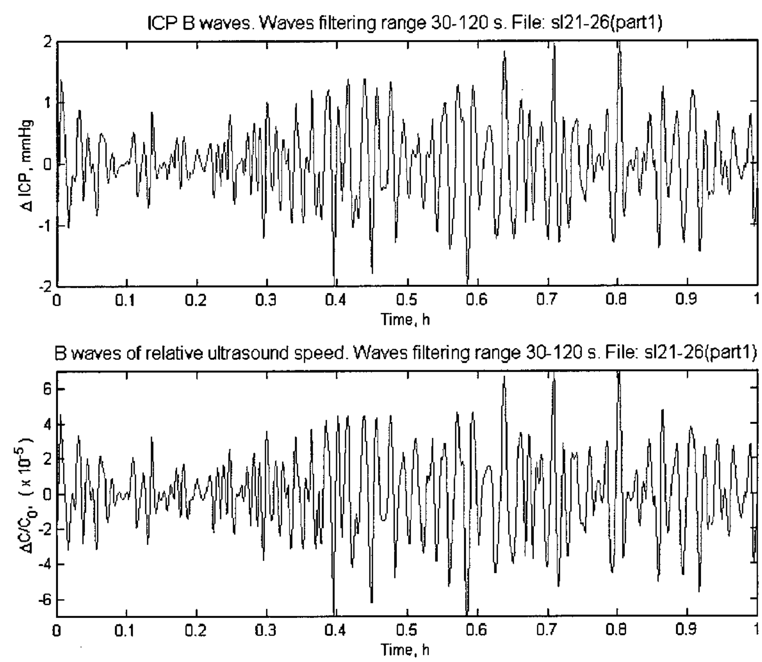
File: rm-v107&v119&v14. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.8972



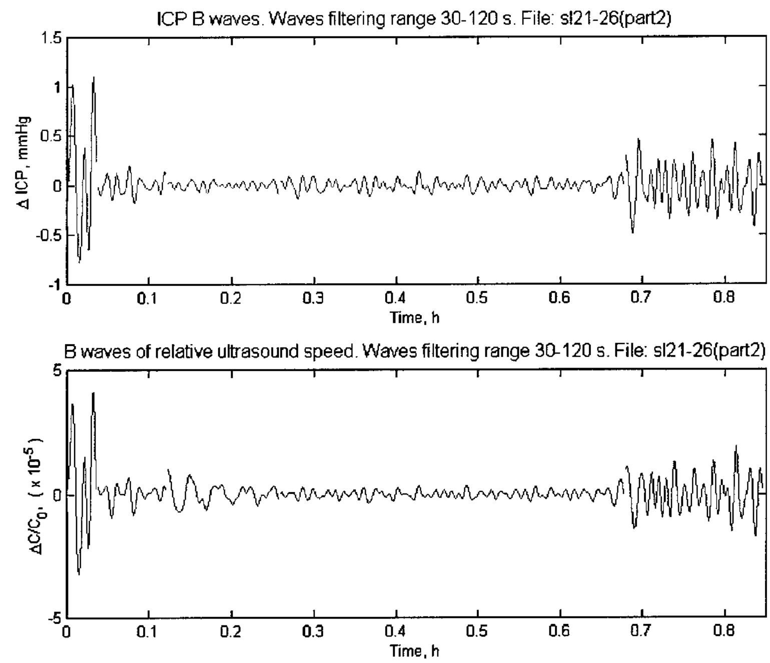
File: sl2-3. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.8834



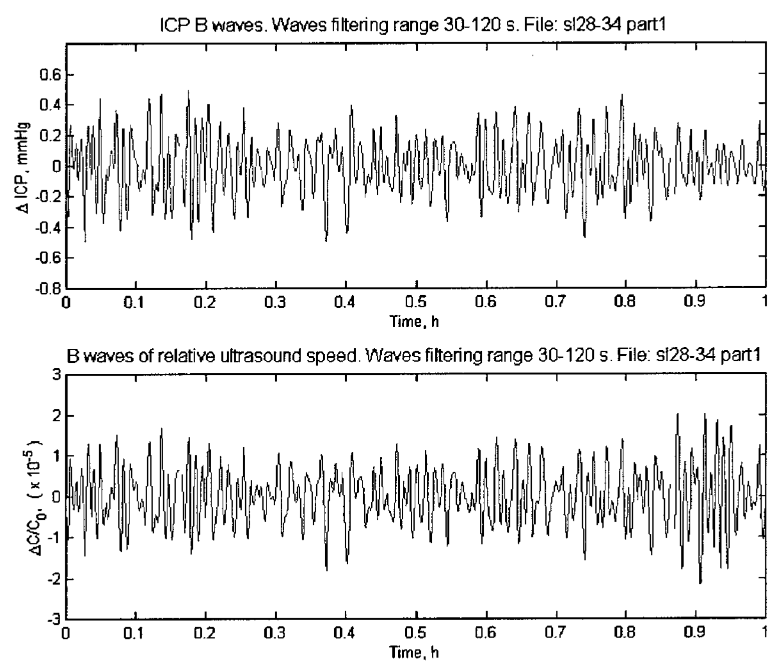
File: sl7. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.8716



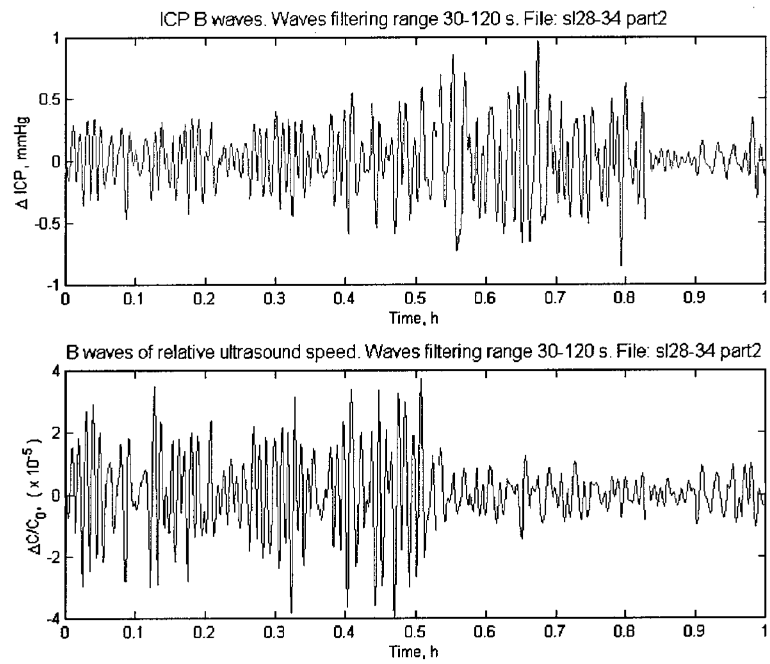
File: sl21_26part1. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.9671



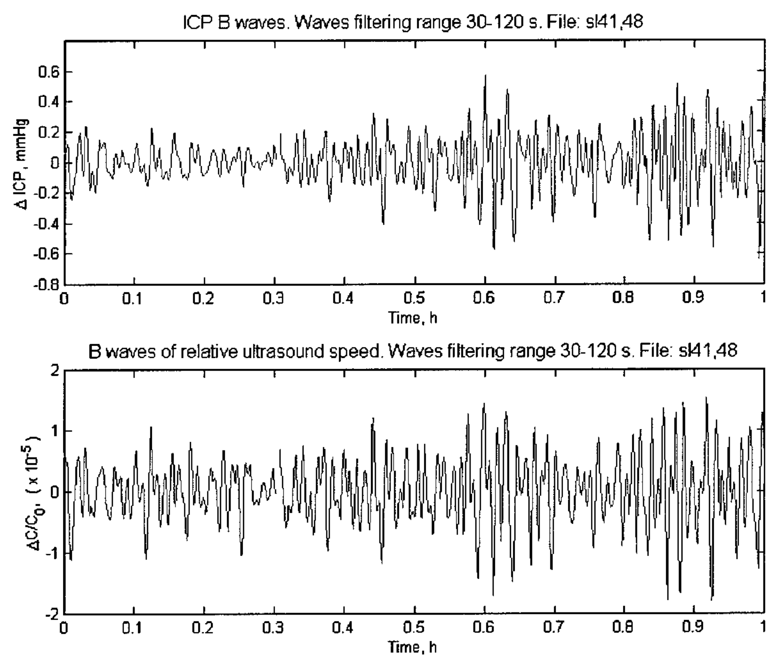
File: sl21_26part2. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.8483



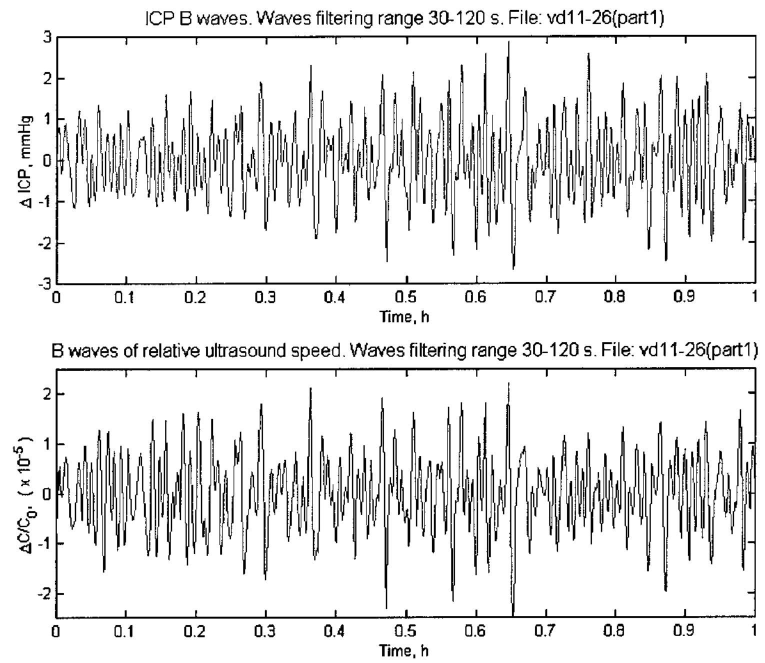
File: sl28-33part1. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.8503



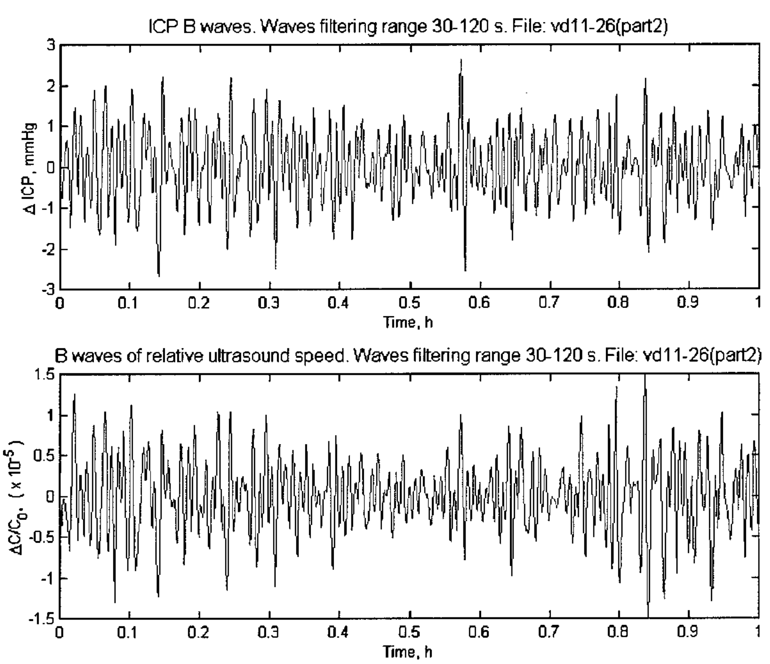
File: sl28-33part2. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.6477



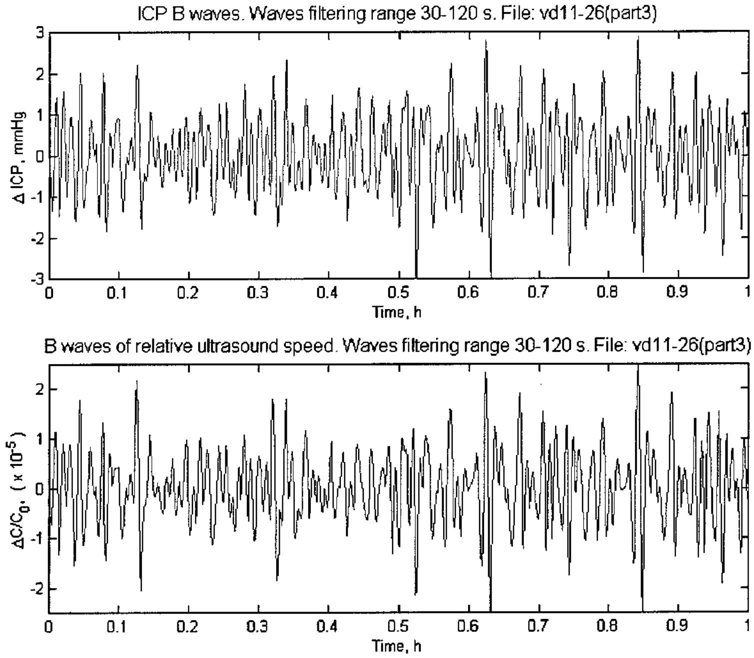
File: sl41&48. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.7322



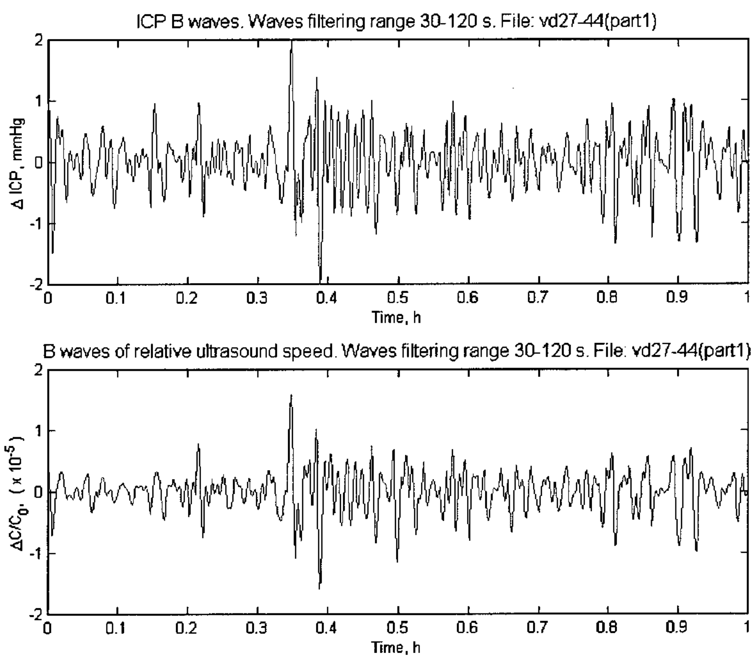
File: vd11_26part1. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.9131



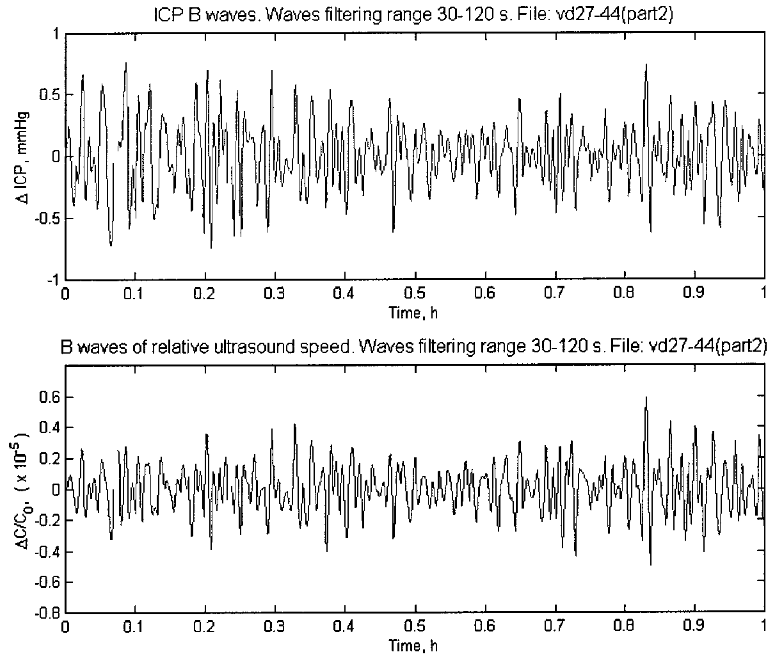
File: vd11_26part2. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.9000



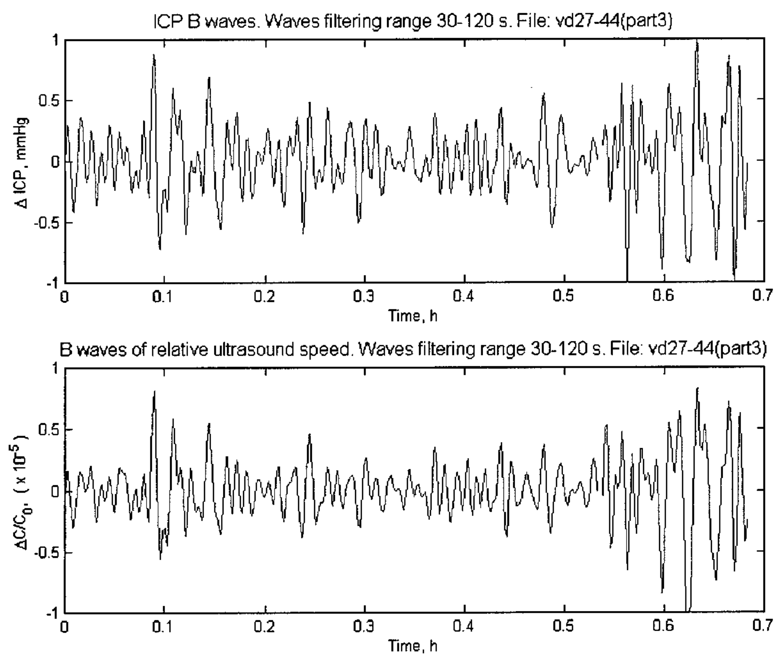
File: vd11_26part3. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.9490



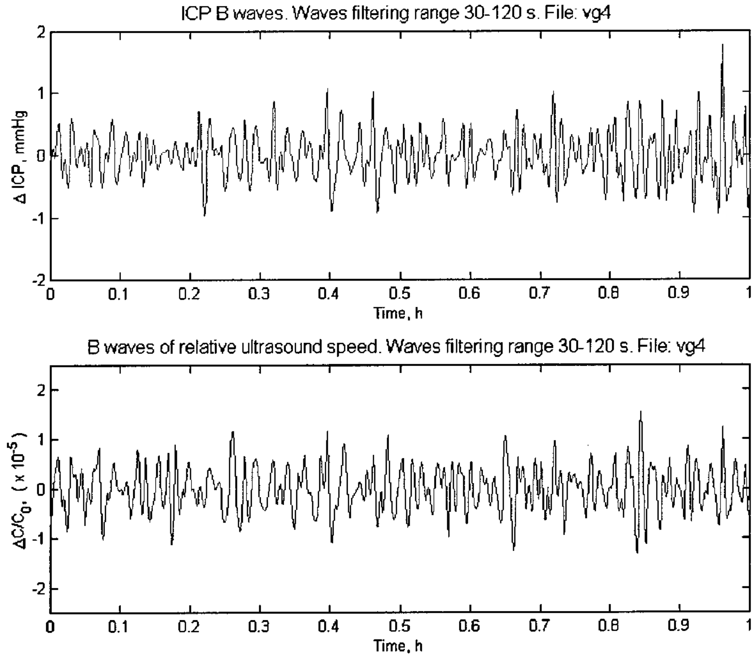
File: vd27_44part1. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.9262



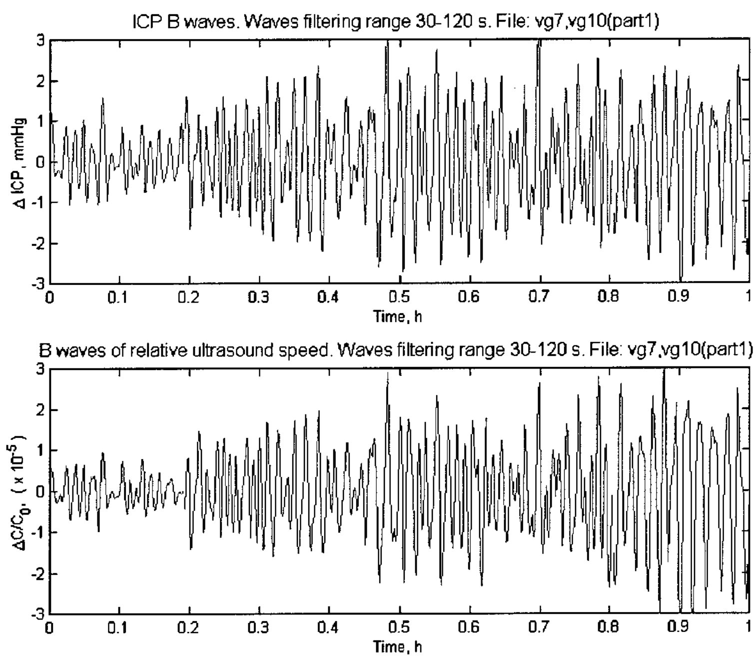
File: vd27_44part2. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.8592



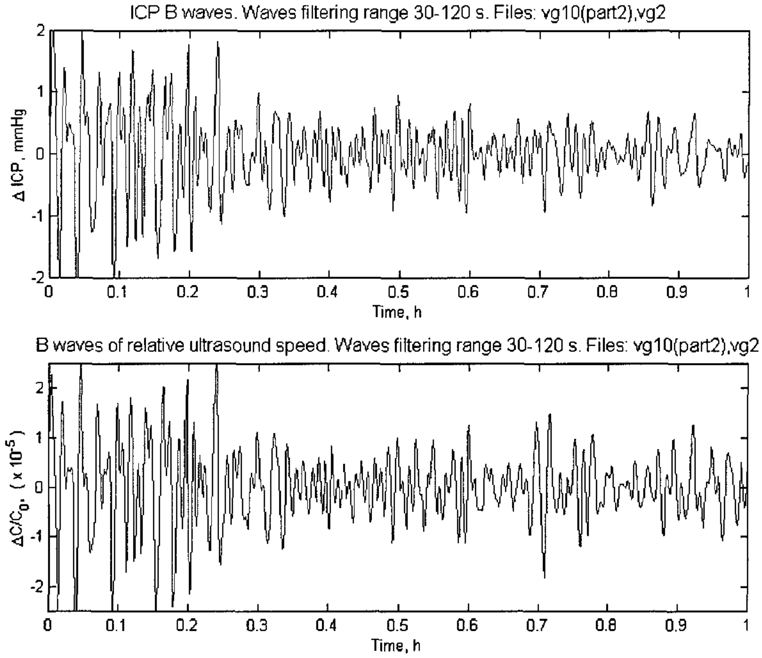
File: vd27_44part3. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.9039



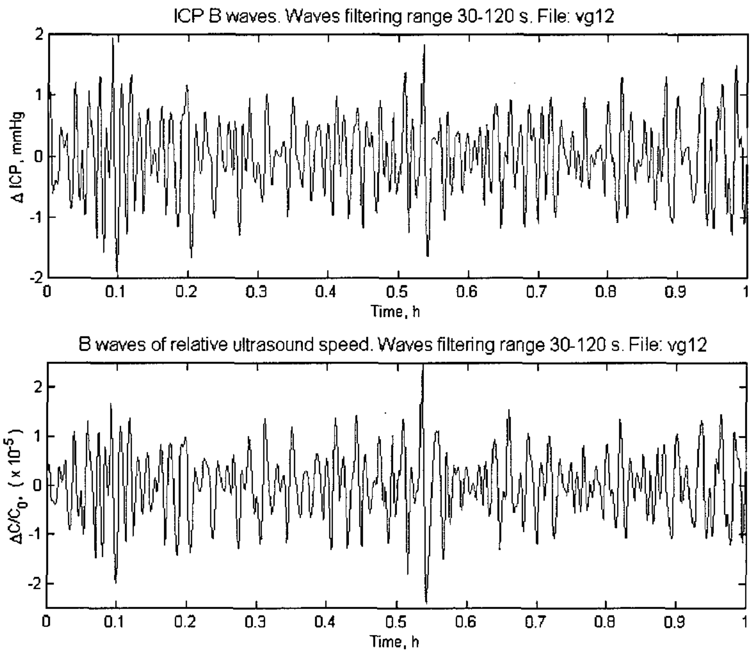
File: vg4. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.6413



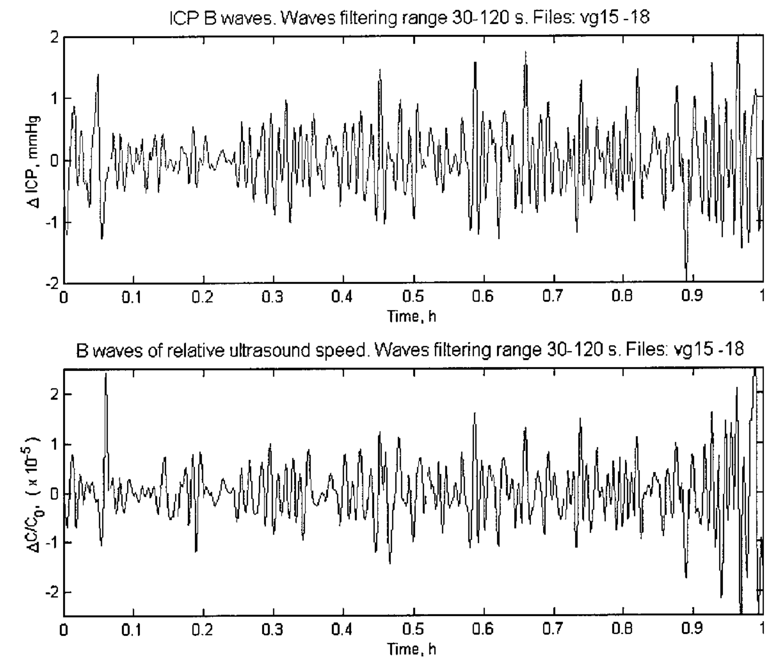
File: vg7&vg10part1. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.8850



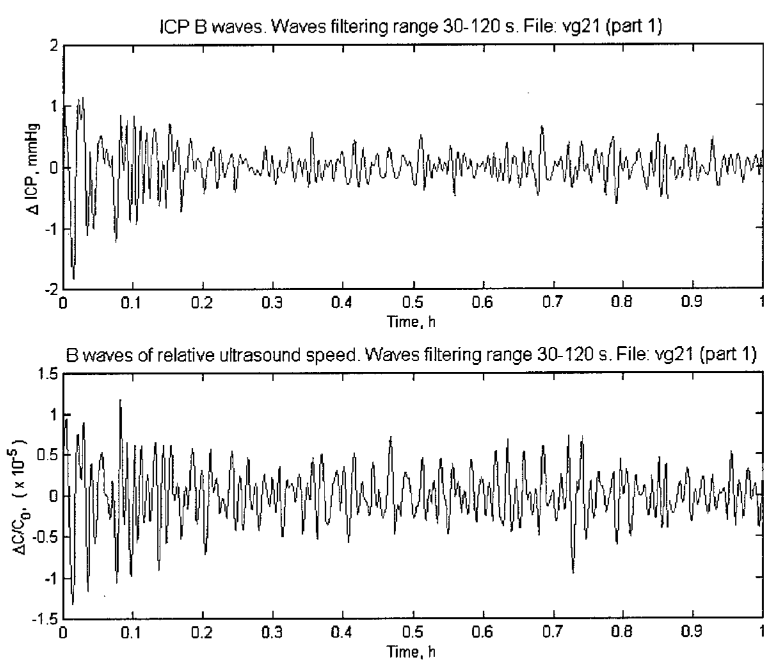
File: vg10part2&vg2. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.8814



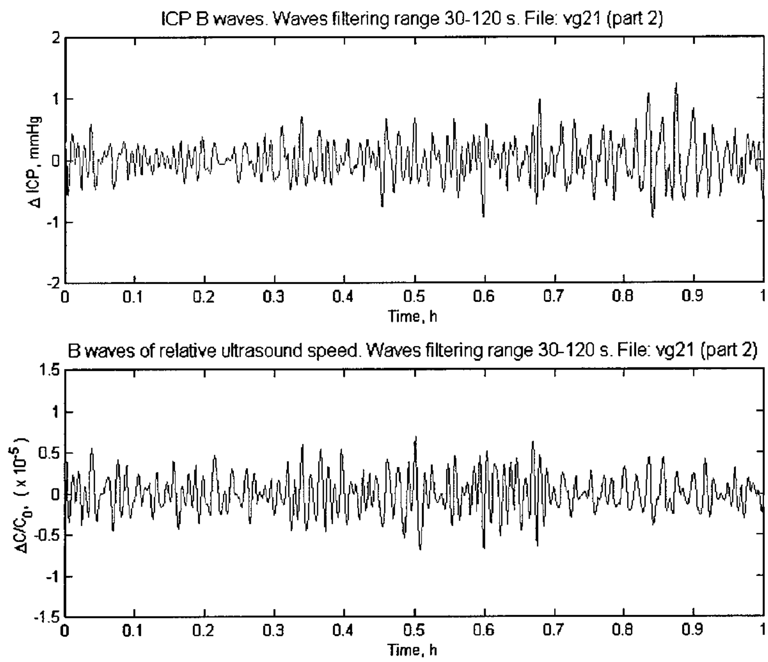
File: vg12. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.9284



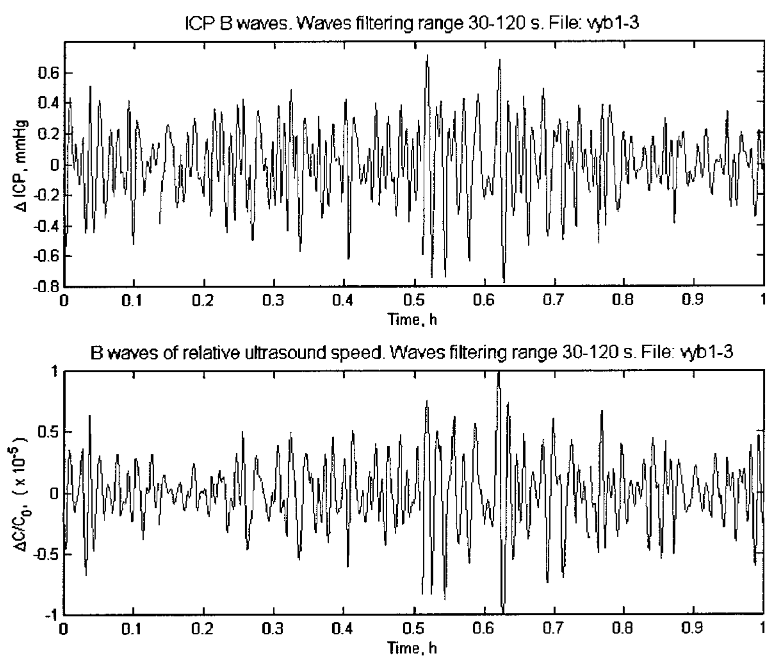
File: vg15&18. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.6107



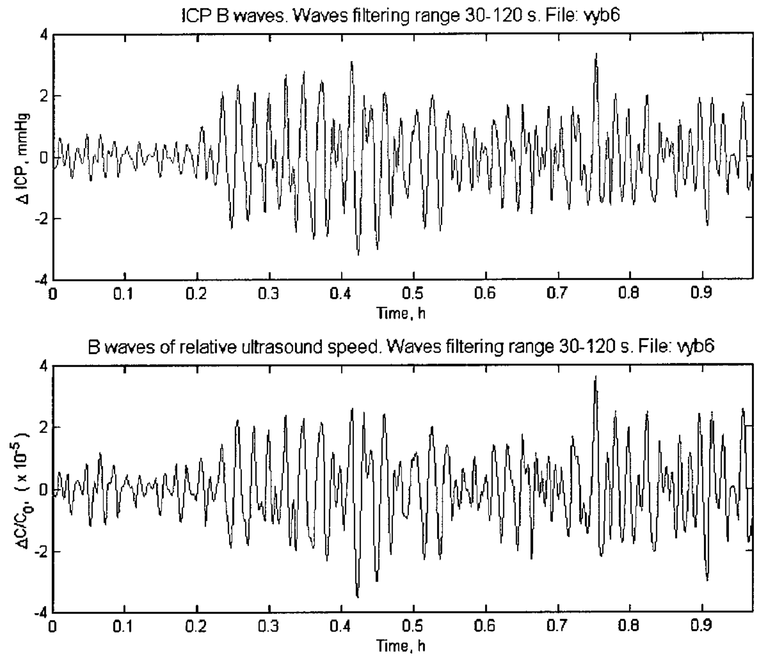
File: vg21part1. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.5719



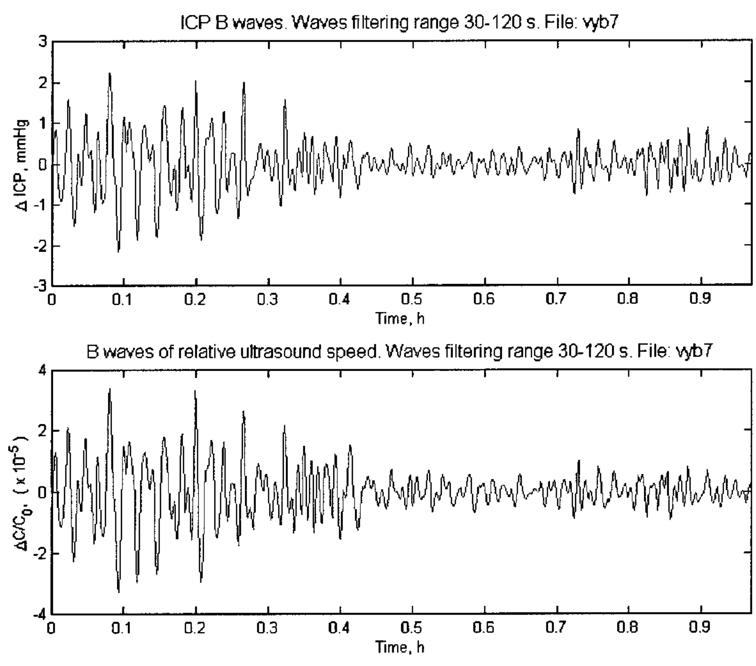
File: vg21part2. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.5411



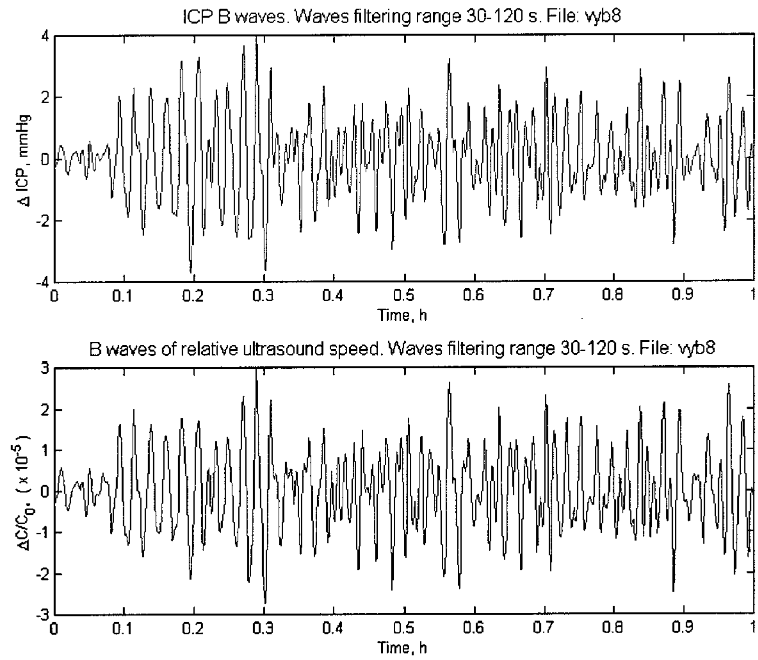
File: vyb1_3. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.8122



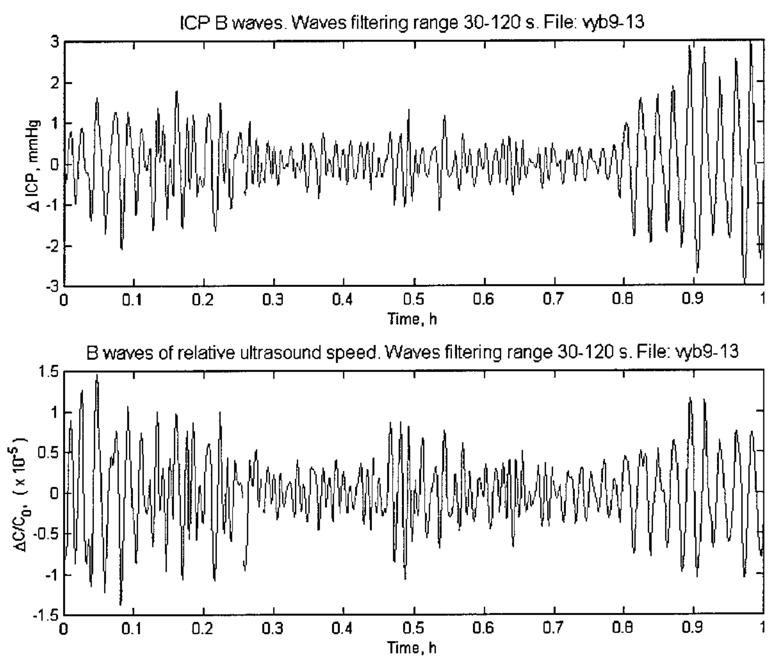
File: vyb6. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.9573



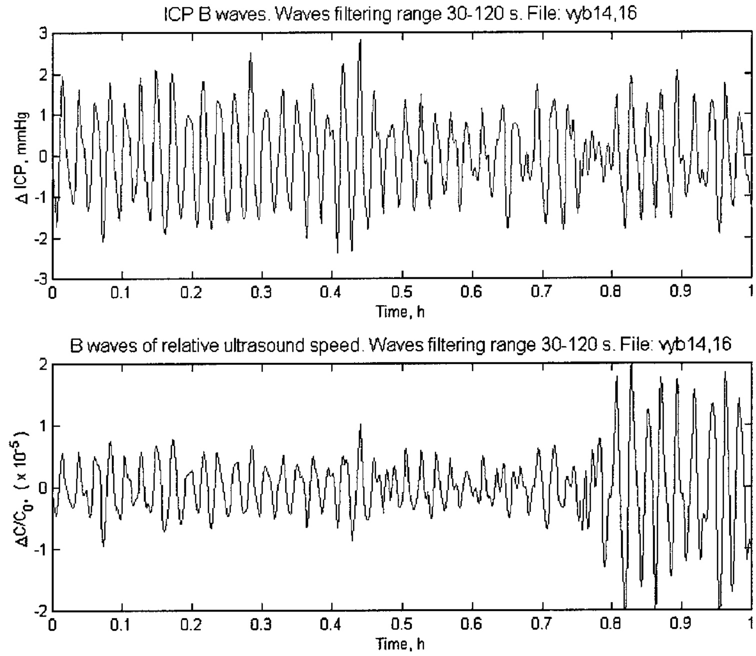
File: vyb7. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.9535



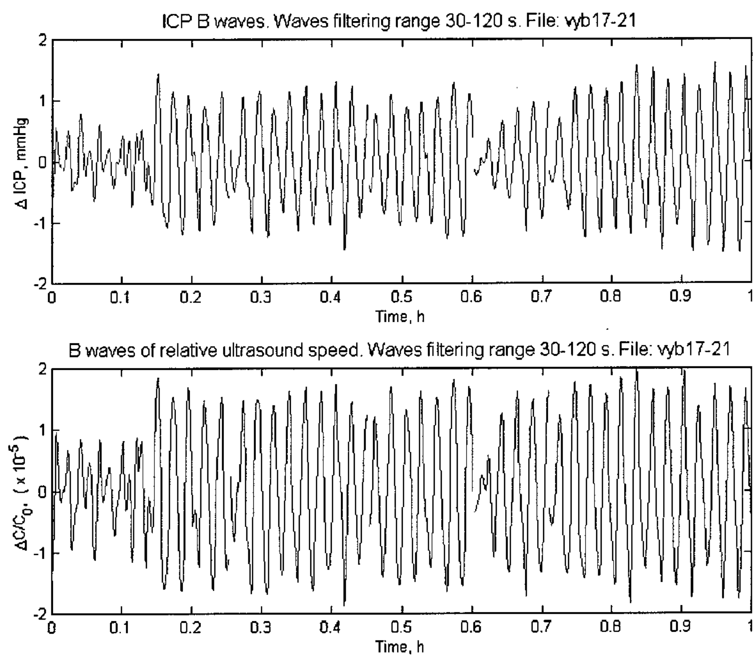
File: vyb8. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.9666



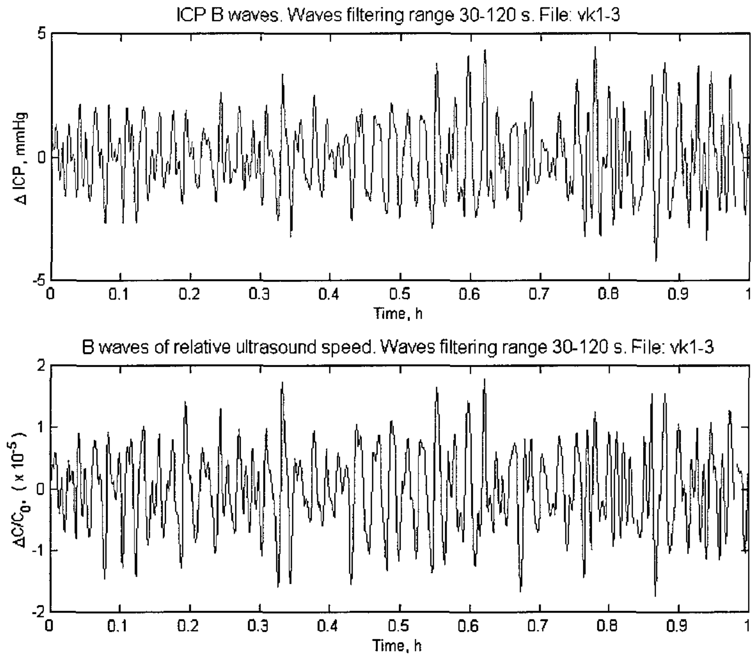
File: vyb9_13. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.8655



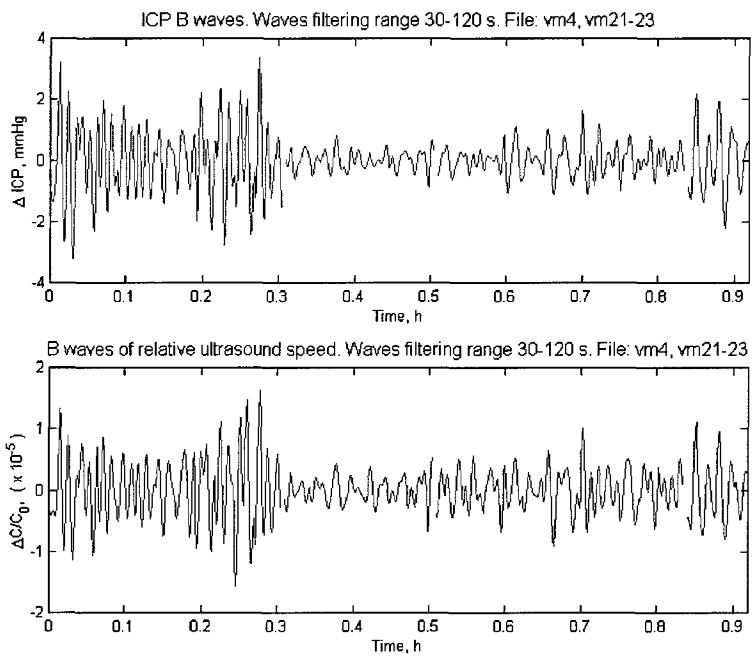
File: vyb14&16. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.7701



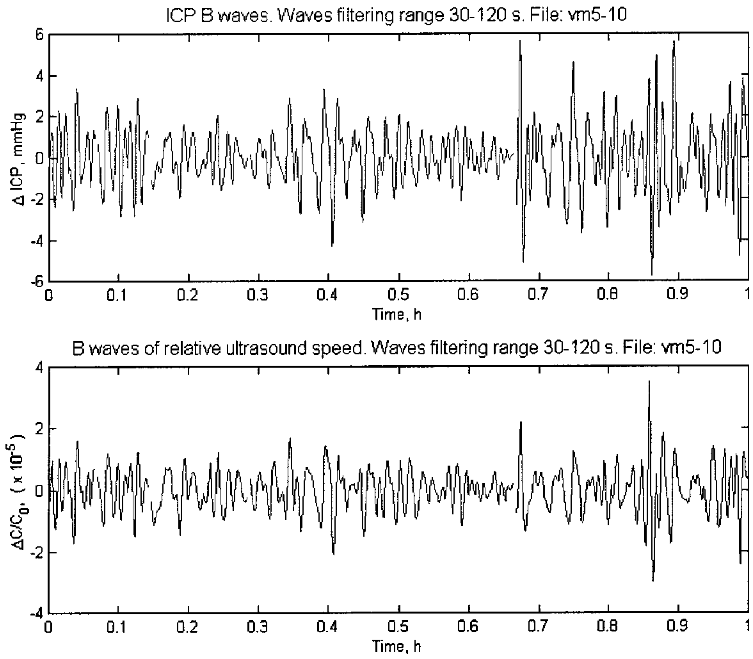
File: vyb17_21. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.9621



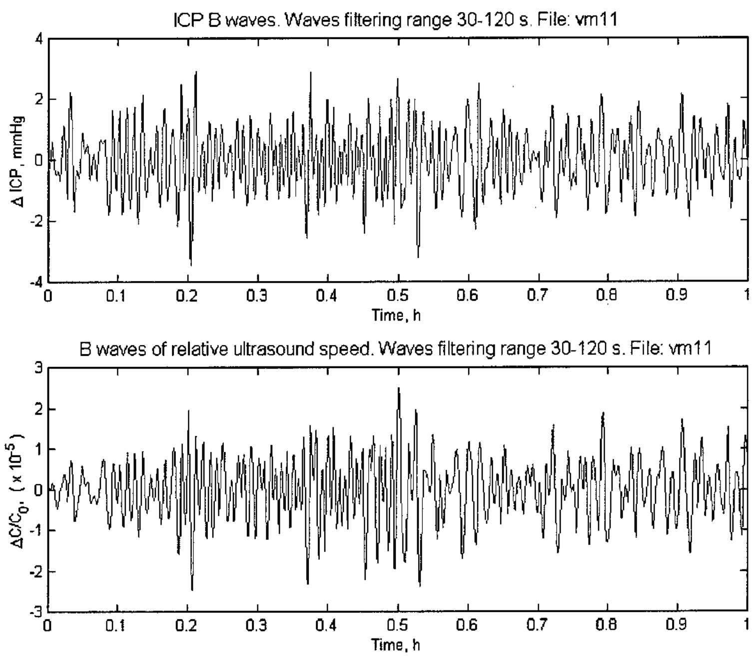
File: vk1_3. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.8131



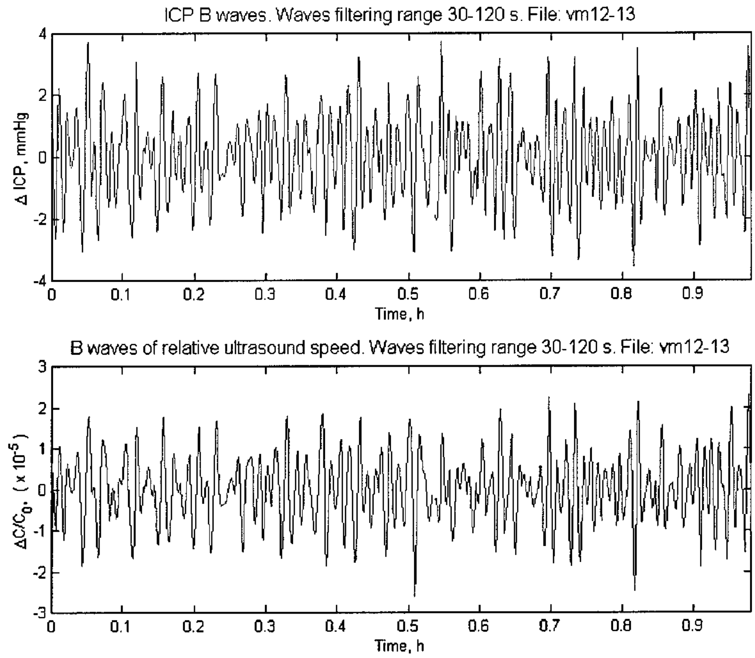
File: vm4&vm21_23. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.6407



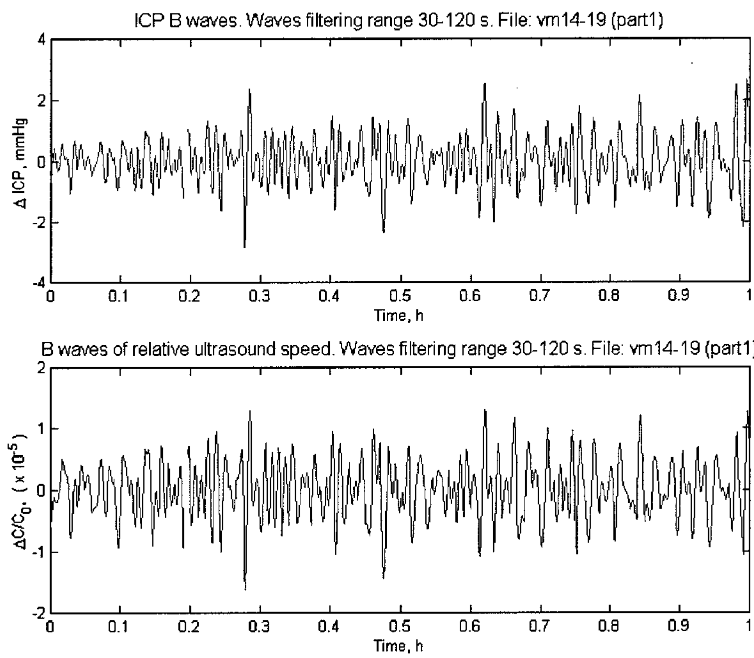
File: vm5_10. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.6445



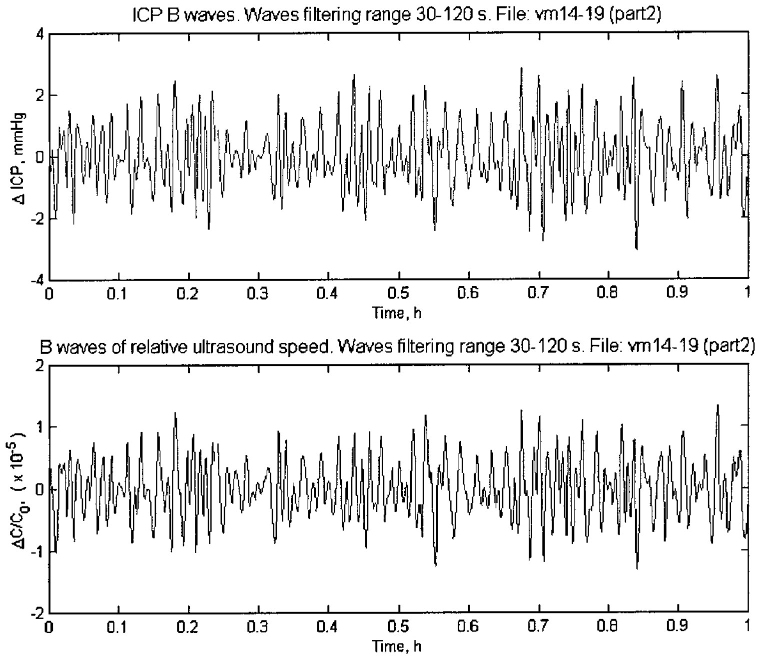
File: vm11. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.5178



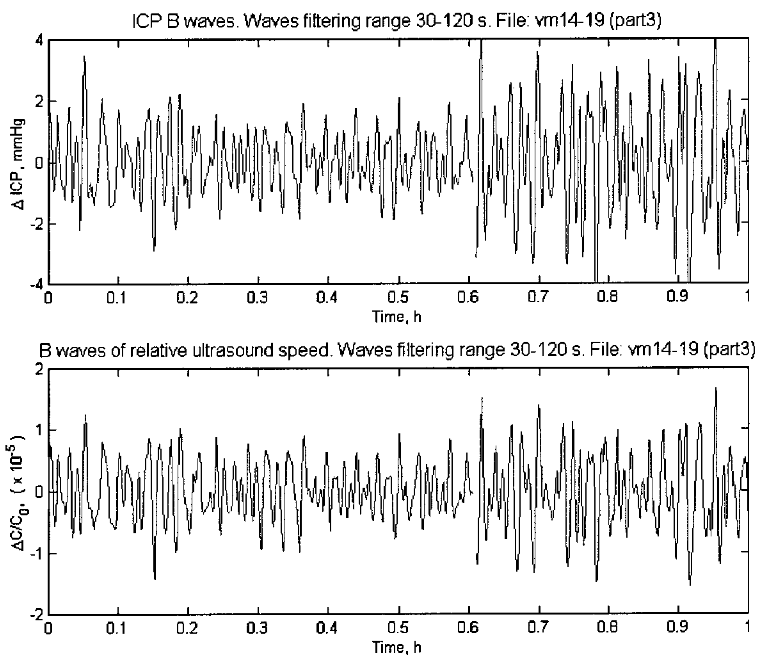
File: vm12. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.6378



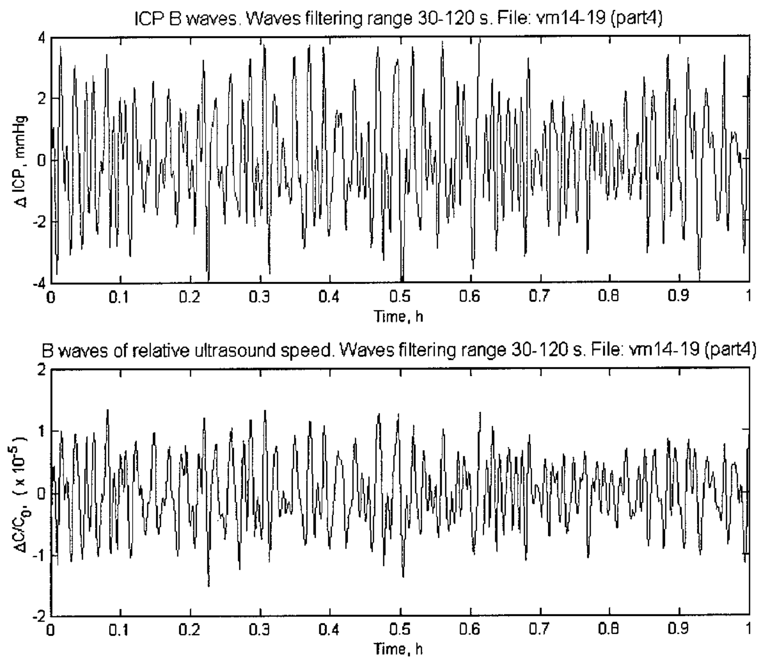
File: vm14_17part1. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.8442



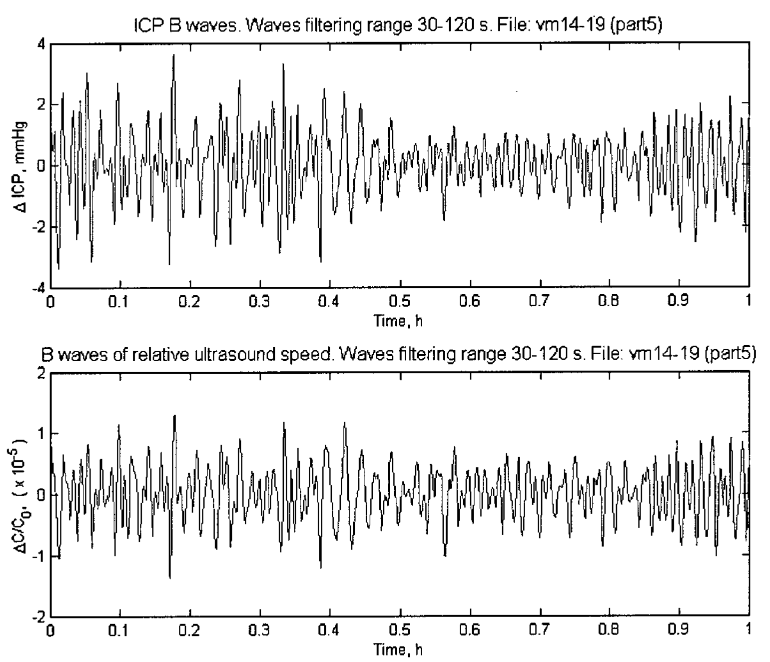
File: vm14_17part2. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.8574



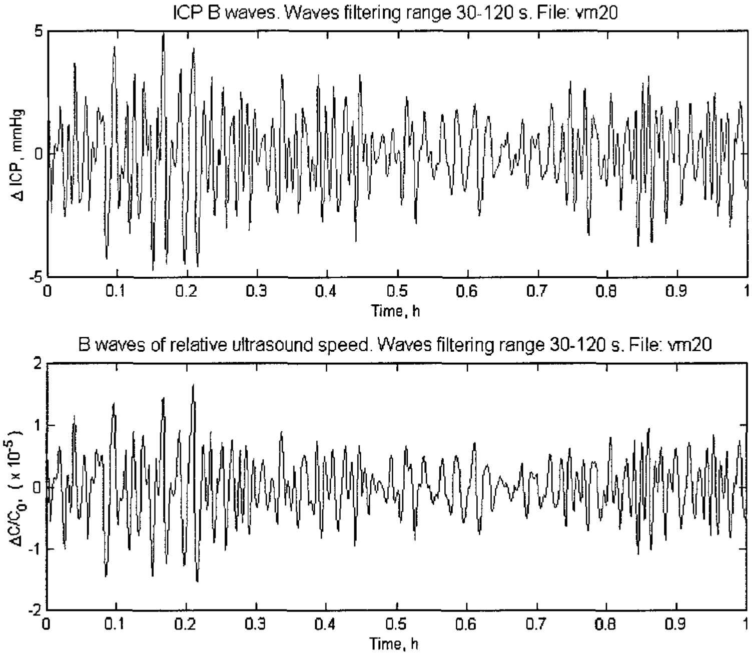
File: vm14_17part3. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.8428



File: vm14_17part4. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.8334



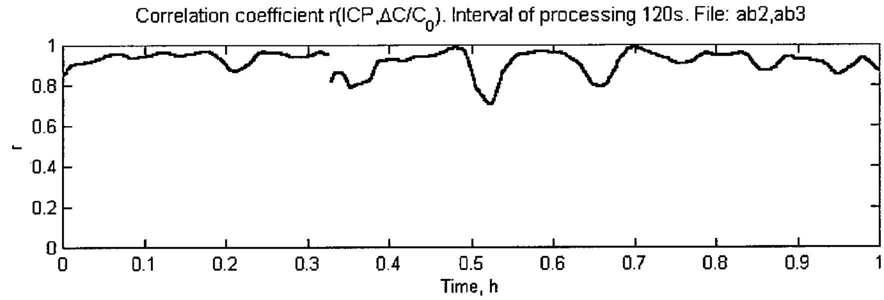
File: vm14_17part5. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.7881

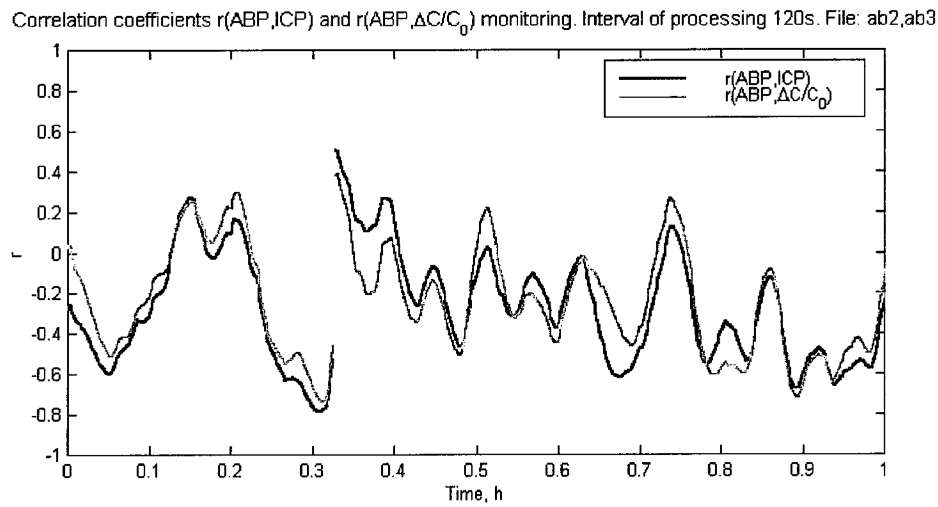


File: vm20. Correlation coefficient r(ICP, $\Delta C/C_0$) = 0.8462

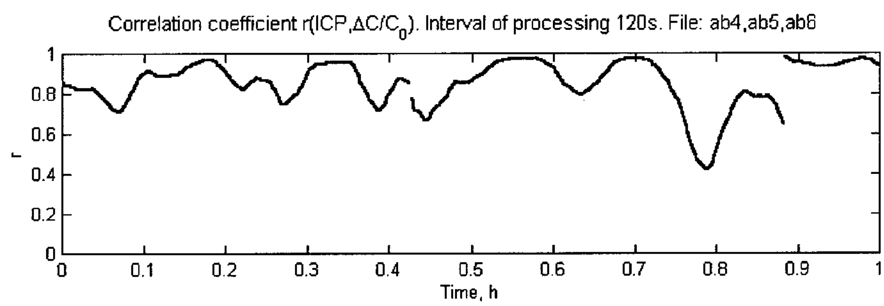
APPENDIX C

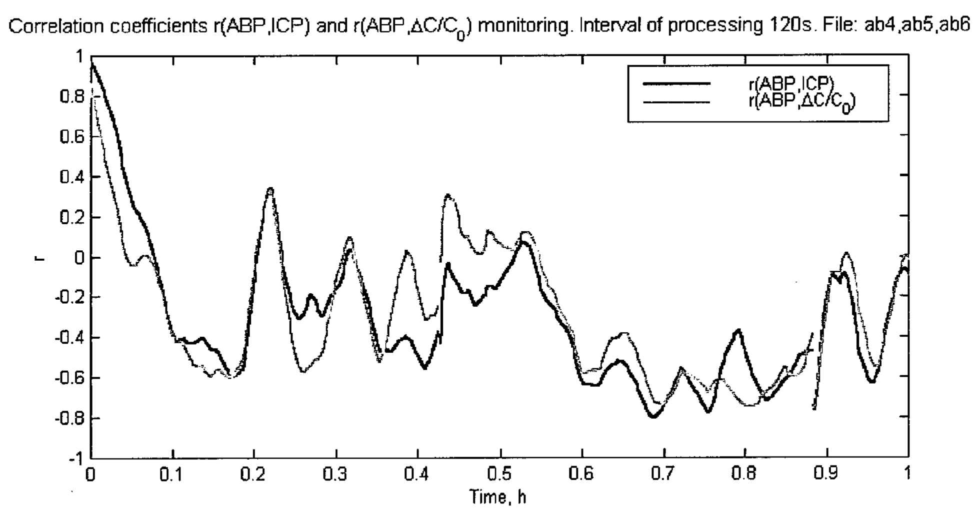
CLINICAL RESULTS OF SIMULTANEOUS INVASIVE AND NON-INVASIVE CEREBROVASCULAR AUTOREGULATION STATE MONITORING



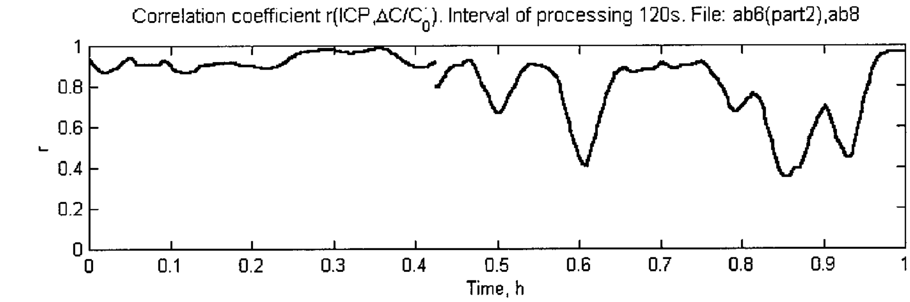


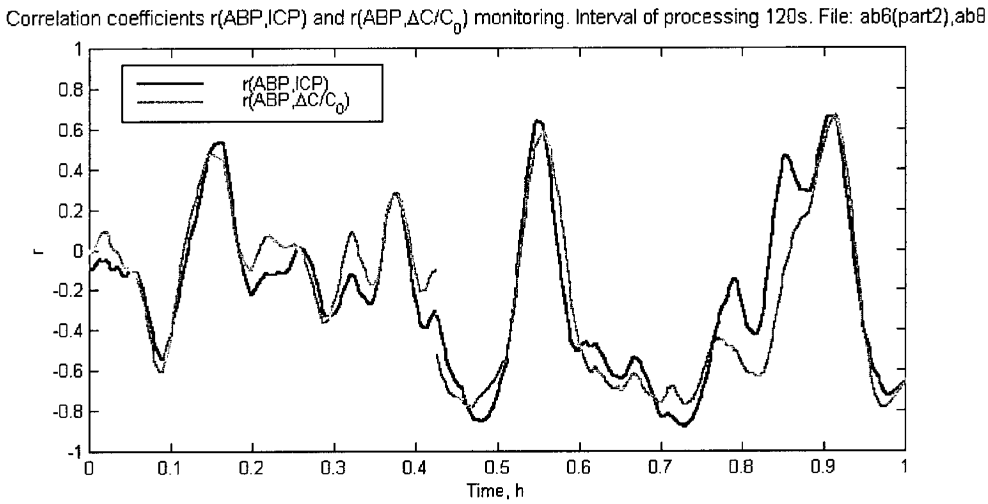
Statistical processing of r(ABP,ICP) and r(ABP,$\Delta C/C_0$): m=703, mD=0.0097, S=0.1411, R=0.9333



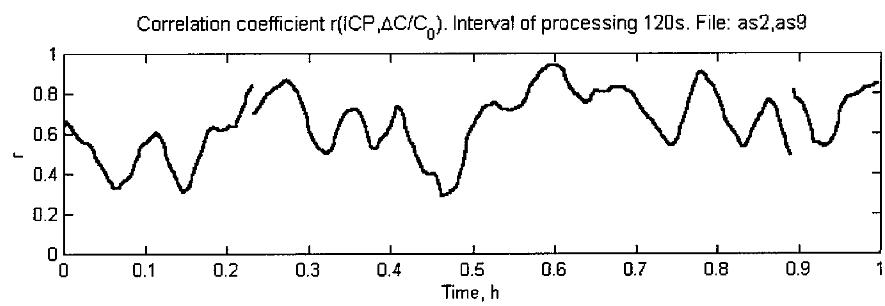


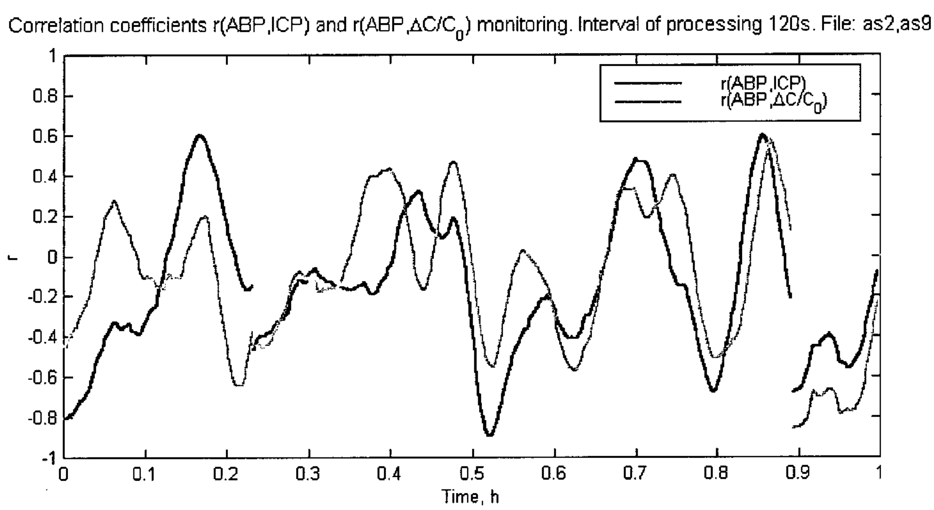
Statistical processing of r(ABP,ICP) and r(ABP,$\Delta C/C_0$): m=703, mD=-0.0175, S=0.1618, R=0.8790



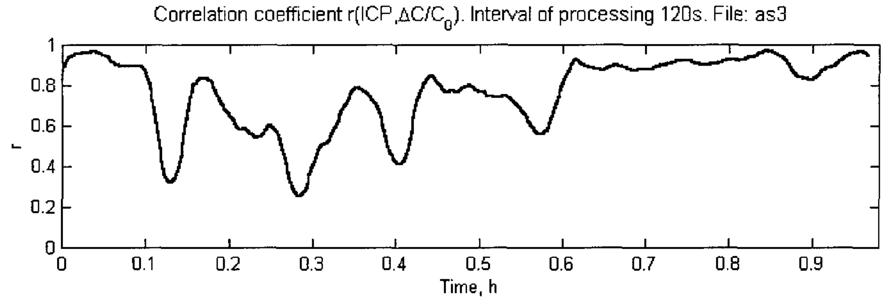


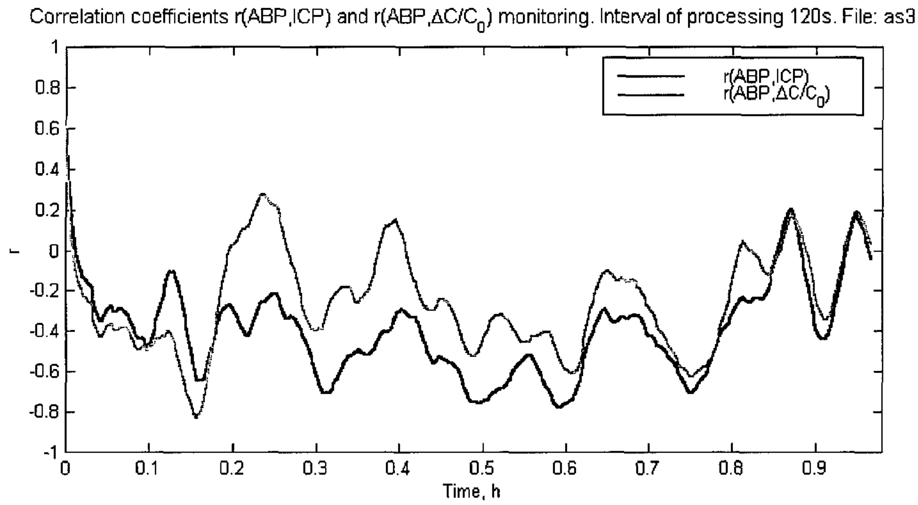
Statistical processing of r(ABP,ICP) and r(ABP,$\Delta C/C_0$): m=703, mD=-0.0268, S=0.1232, R=0.9010



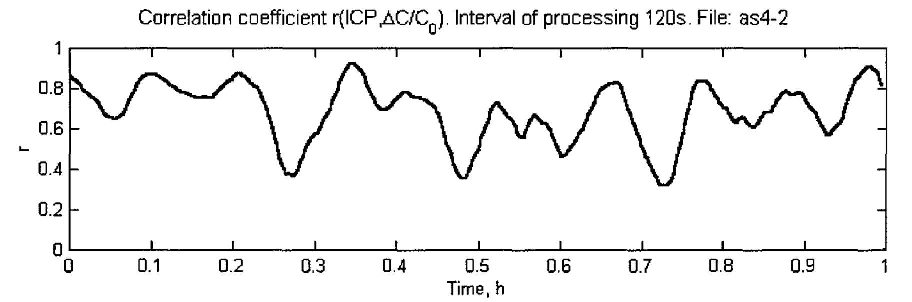


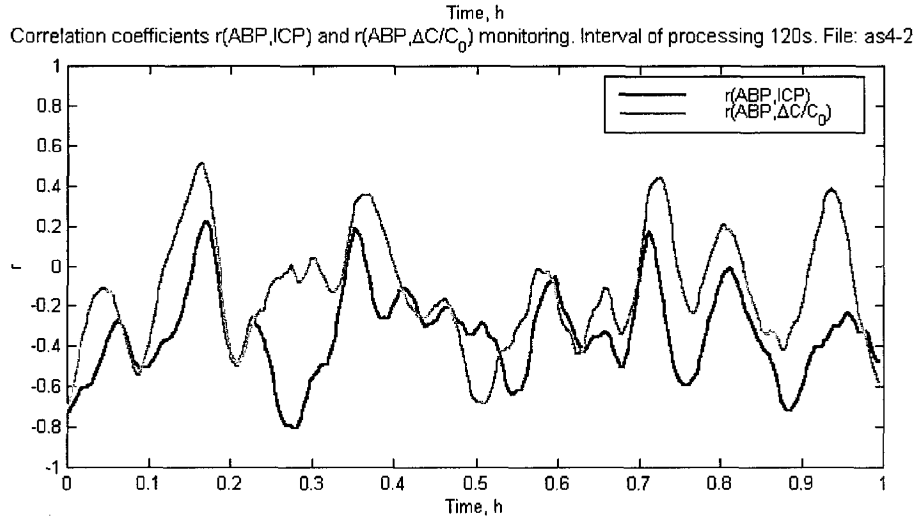
Statistical processing of r(ABP,ICP) and r(ABP,$\Delta C/C_0$): m=700, mD=-0.0409, S=0.3069, R=0.6243





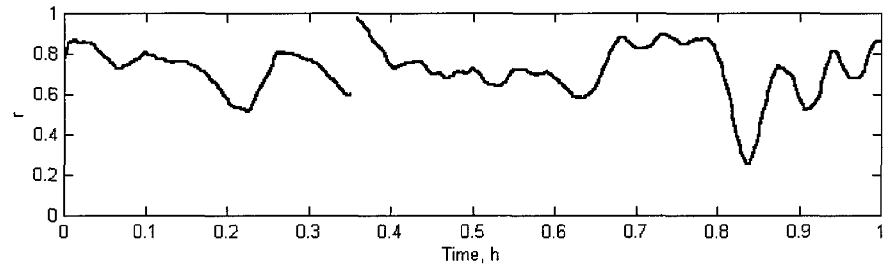
Statistical processing of r(ABP,ICP) and r(ABP,$\Delta C/C_0$): m=681, mD=-0.1451, S=0.1909, R=0.68057



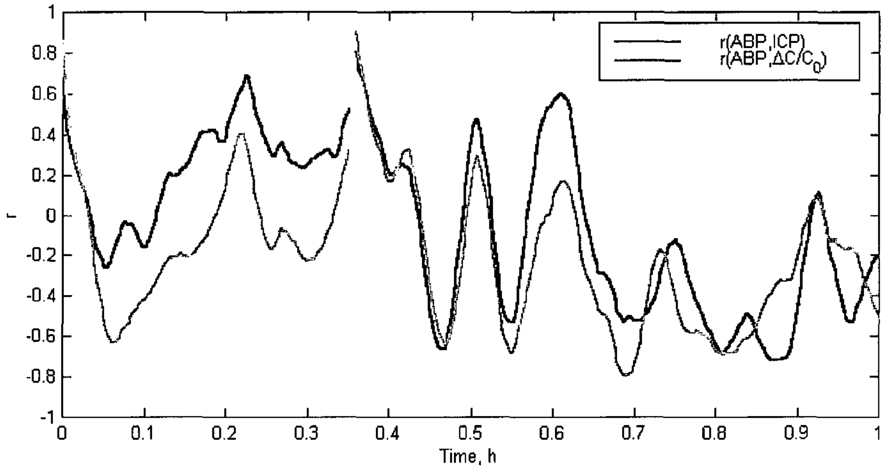


Statistical processing of r(ABP,ICP) and r(ABP,$\Delta C/C_0$): m=703, mD= -0.2203, S=0.2389, R=0.52748

Correlation coefficient r(ICP,$\Delta C/C_0$). Interval of processing 120s. File: as7-1

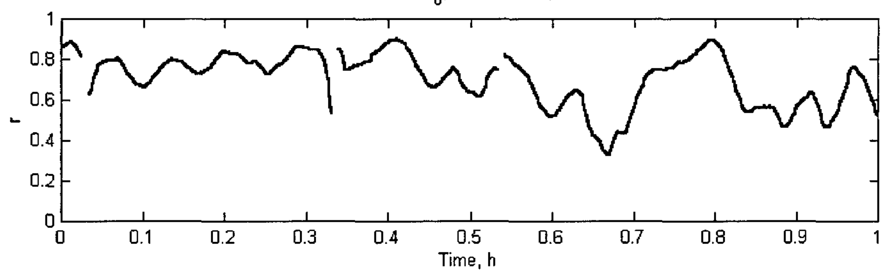


Correlation coefficients r(ABP,ICP) and r(ABP,$\Delta C/C_0$) monitoring. Interval of processing 120s. File: as7-1

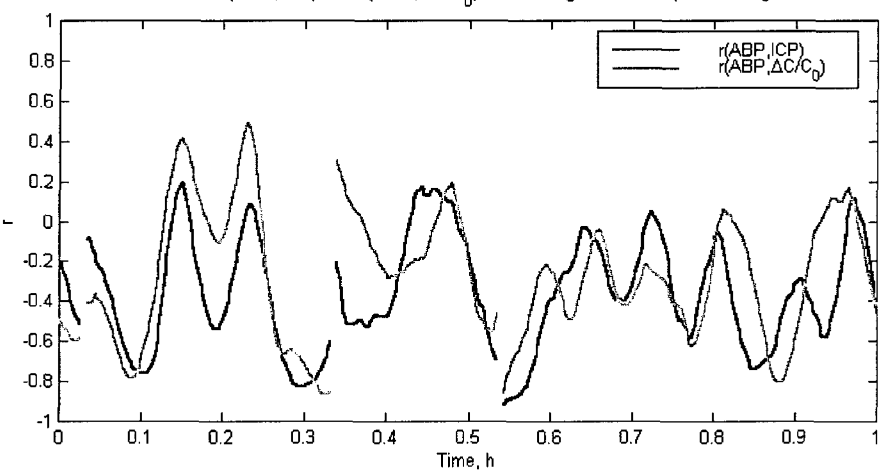


Statistical processing of r(ABP,ICP) and r(ABP,$\Delta C/C_0$): m=703, mD= 0.1680, S= 0.2339, R= 0.8134

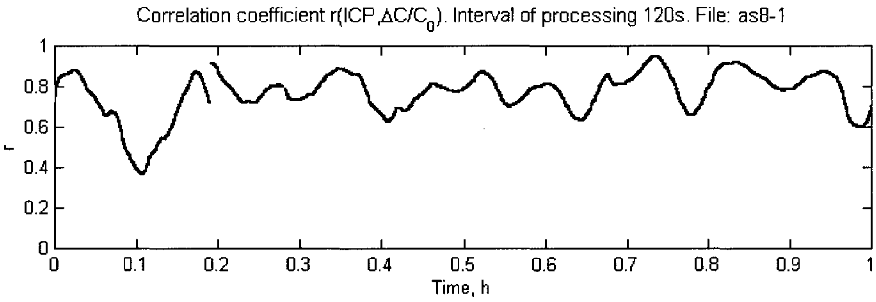
Correlation coefficient r(ICP,$\Delta C/C_0$). Interval of processing 120s. File: as7-2

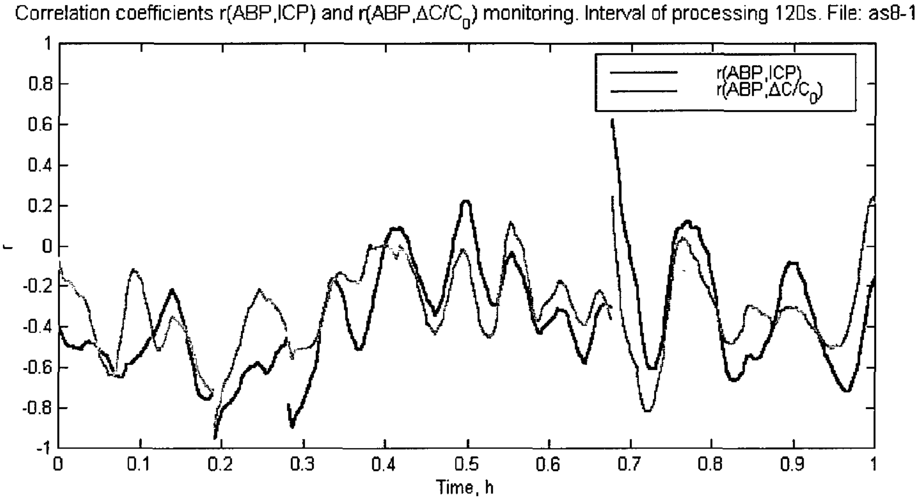


Correlation coefficients r(ABP,ICP) and r(ABP,$\Delta C/C_0$) monitoring. Interval of processing 120s. File: as7-2

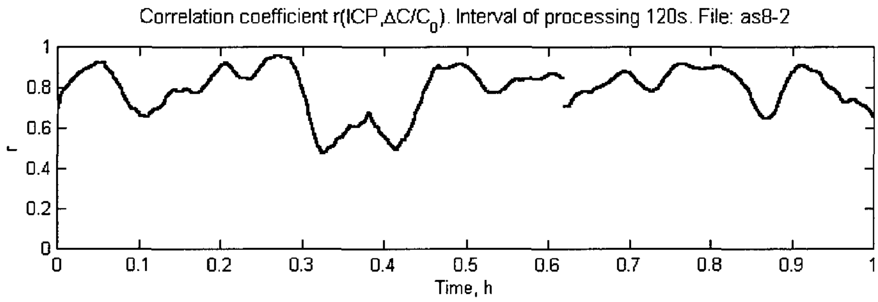


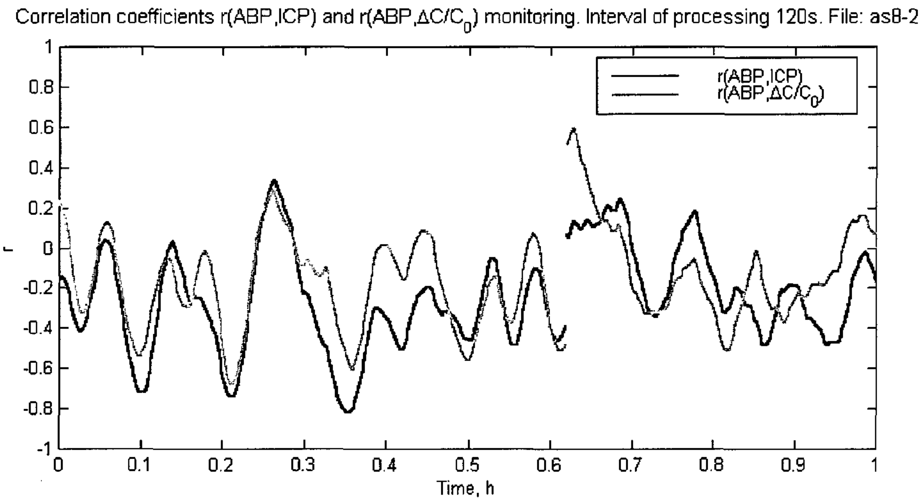
Statistical processing of r(ABP,ICP) and r(ABP,$\Delta C/C_0$): m=703, mD= -0.0847, S= 0.2325, R= 0.6796



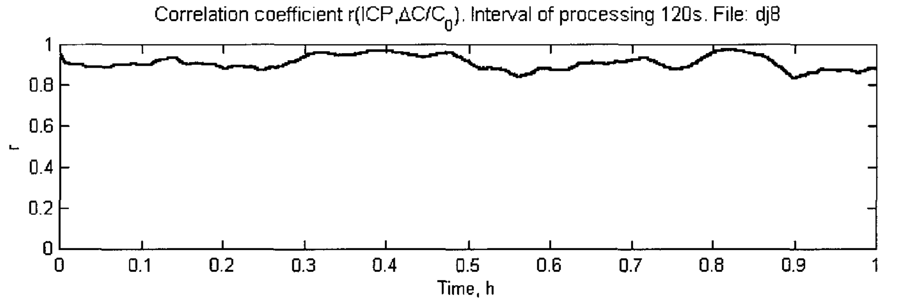


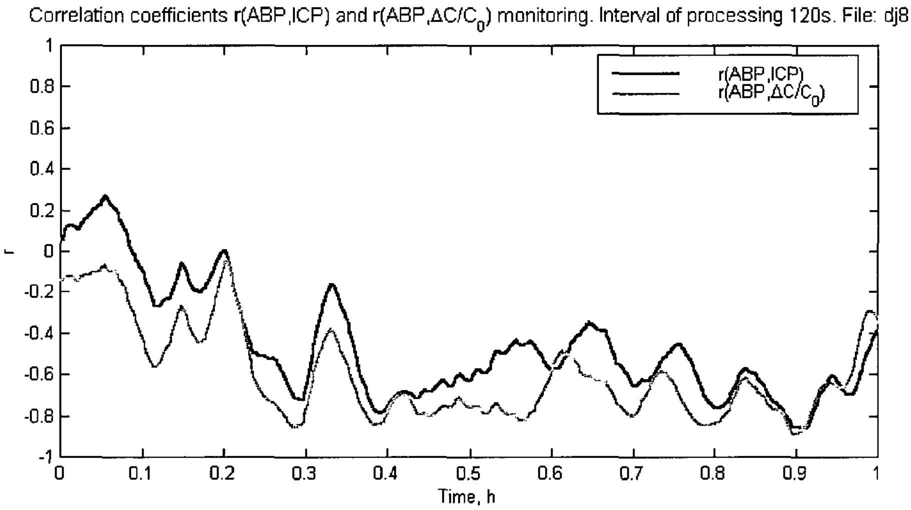
Statistical processing of r(ABP,ICP) and r(ABP,$\Delta C/C_0$): m=703, mD= -0.0474, S= 0.1899, R= 0.6365



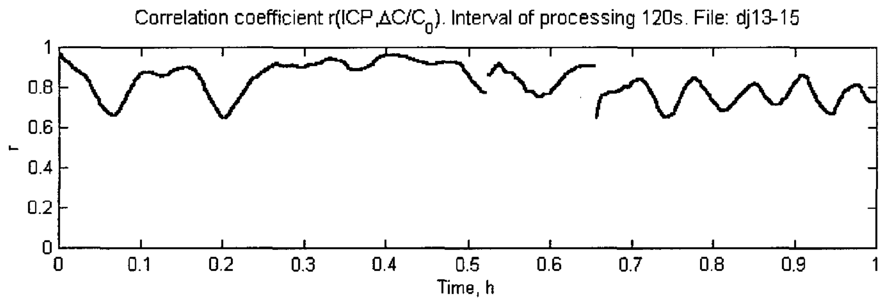


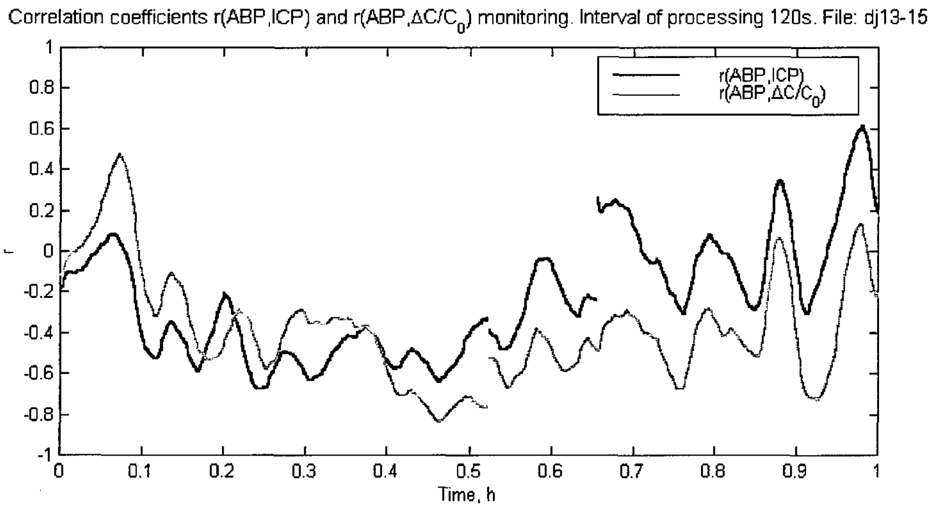
Statistical processing of r(ABP,ICP) and r(ABP,$\Delta C/C_0$): m=703, mD= -0.0793, S= 0.1680, R= 0.7393



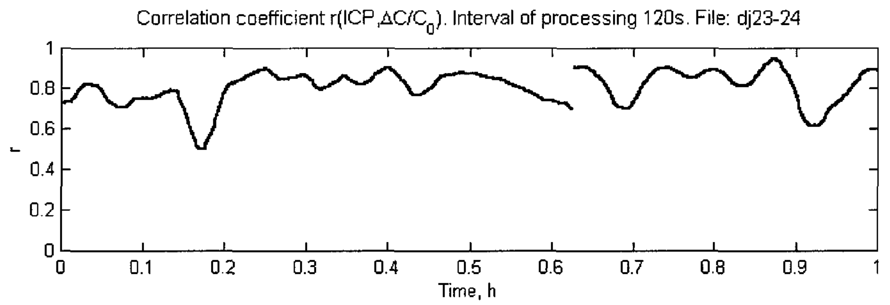


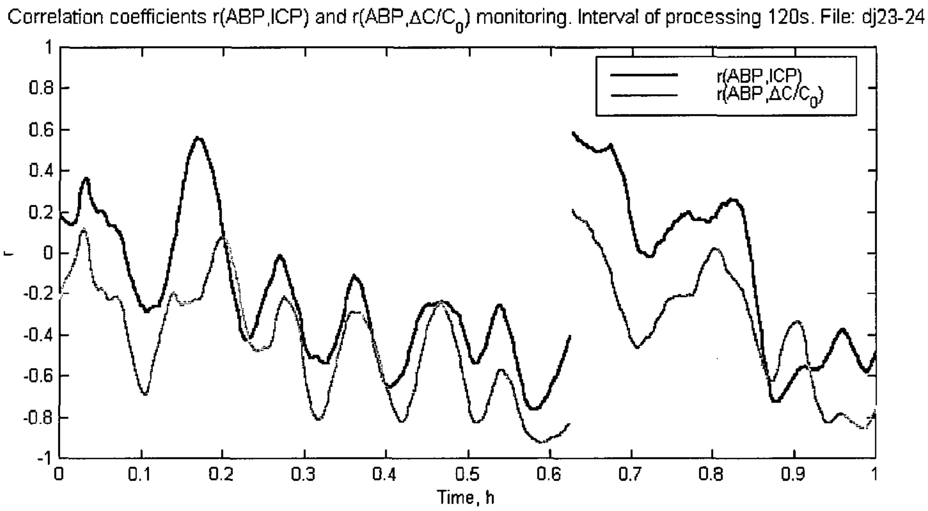
Statistical processing of r(ABP,ICP) and r(ABP,ΔC/C$_0$): m=703, mD=0.1404, S=0.1191, R=0.9044



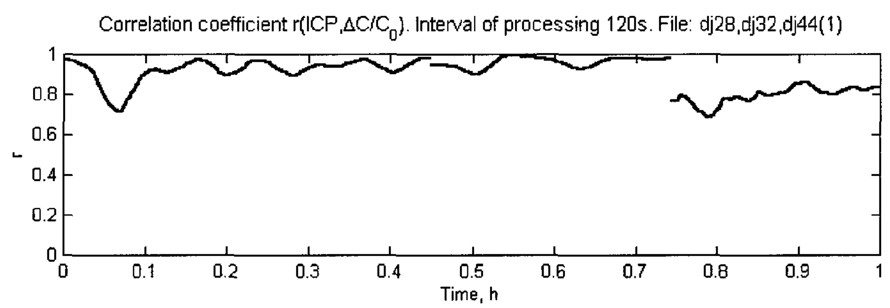


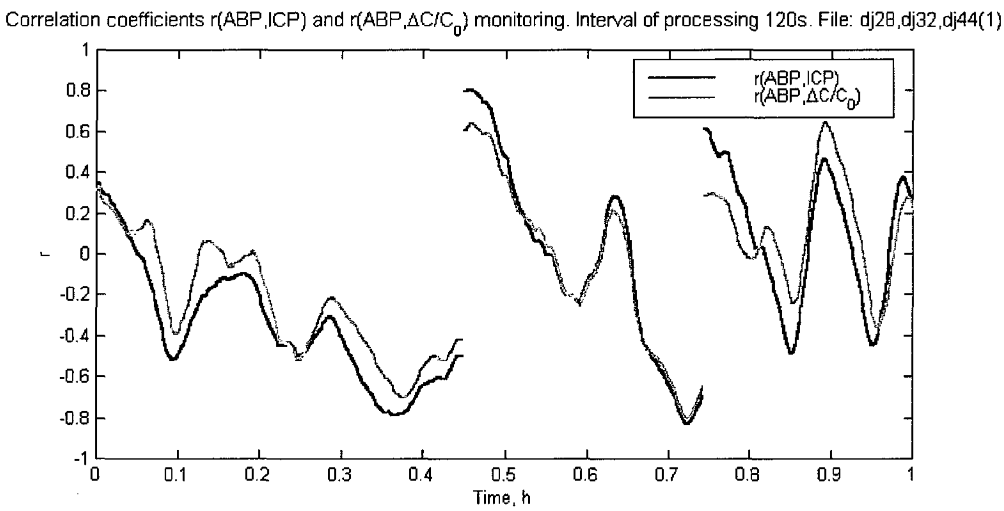
Statistical processing of r(ABP,ICP) and r(ABP,ΔC/C$_0$): m=703, mD=0.1488, S=0.2760, R=0.5239





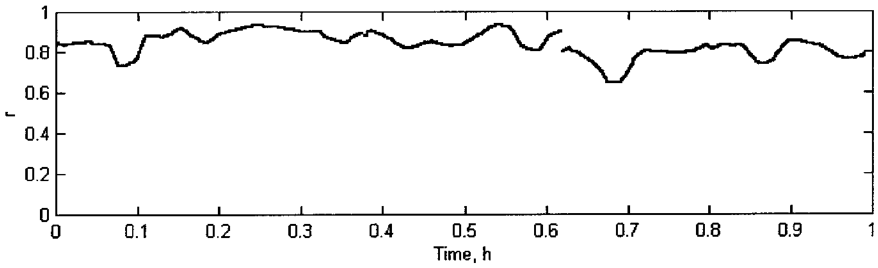
Statistical processing of r(ABP,ICP) and r(ABP,ΔC/C₀): m=703, mD=0.2504, S=0.1961, R=0.8465



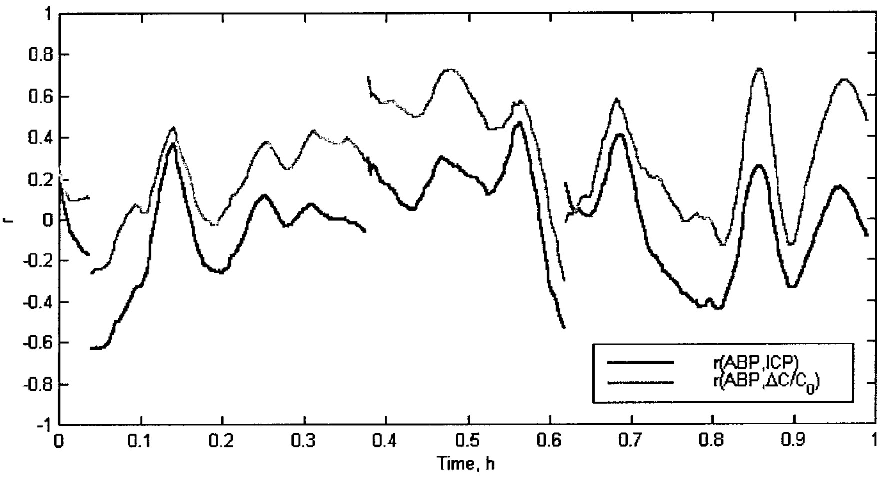


Statistical processing of r(ABP,ICP) and r(ABP,ΔC/C₀): m=703, mD=-0.0462, S=0.1445, R=0.9414

Correlation coefficient r(ICP,$\Delta C/C_0$). Interval of processing 120s. File: dj44(2),dj47-52

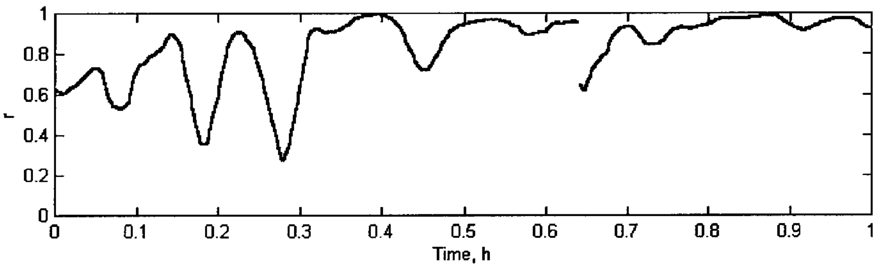


Correlation coefficients r(ABP,ICP) and r(ABP,$\Delta C/C_0$) monitoring. Interval of processing 120s. File: dj44(2),dj47-52

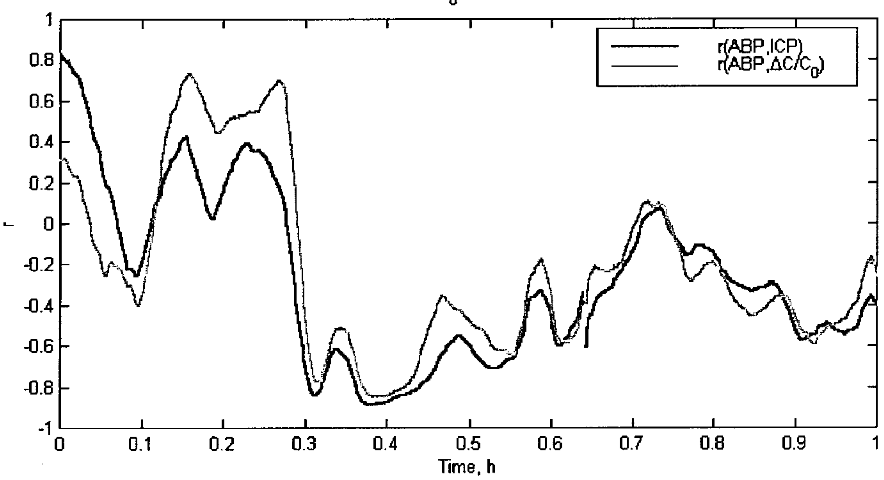


Statistical processing of r(ABP,ICP) and r(ABP,$\Delta C/C_0$): m=698, mD=-0.3114, S=0.1216, R=0.8806

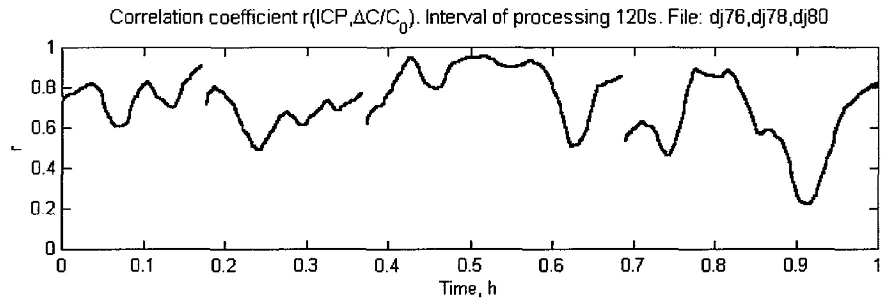
Correlation coefficient r(ICP,$\Delta C/C_0$). Interval of processing 120s. File: dj57,dj59

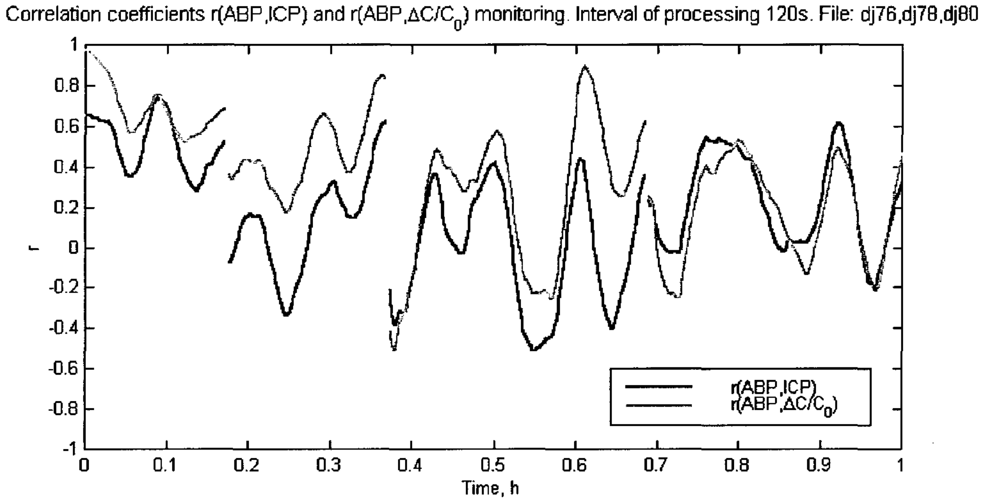


Correlation coefficients r(ABP,ICP) and r(ABP,$\Delta C/C_0$) monitoring. Interval of processing 120s. File: dj57,dj59

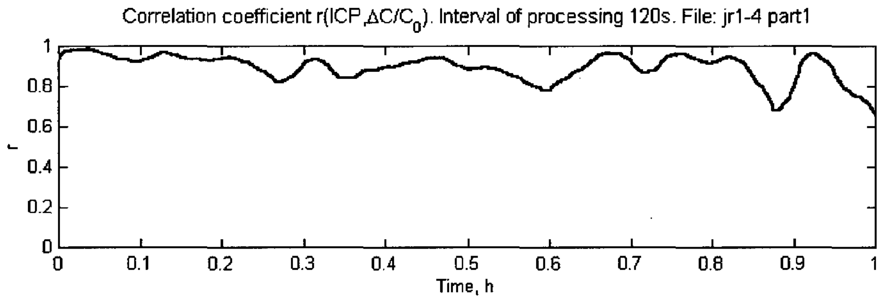


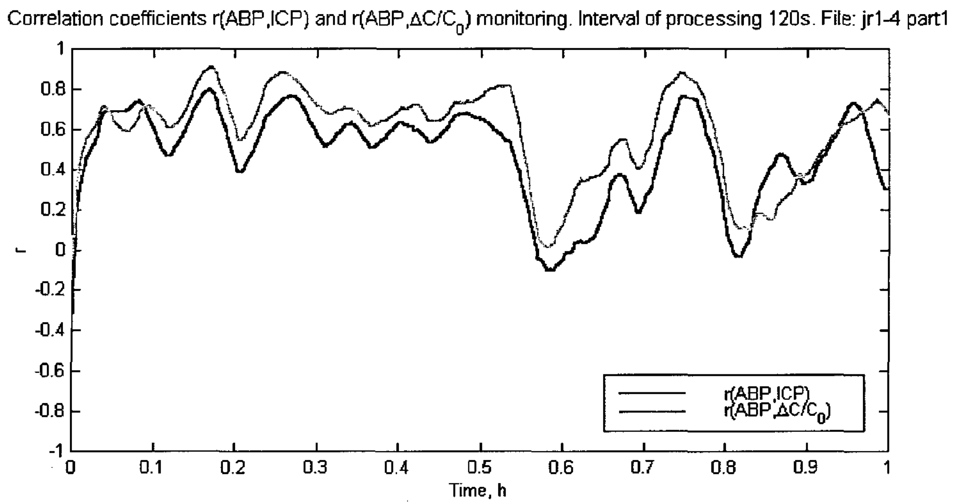
Statistical processing of r(ABP,ICP) and r(ABP,$\Delta C/C_0$): m=703, mD=-0.0560, S=0.2092, R=0.8743



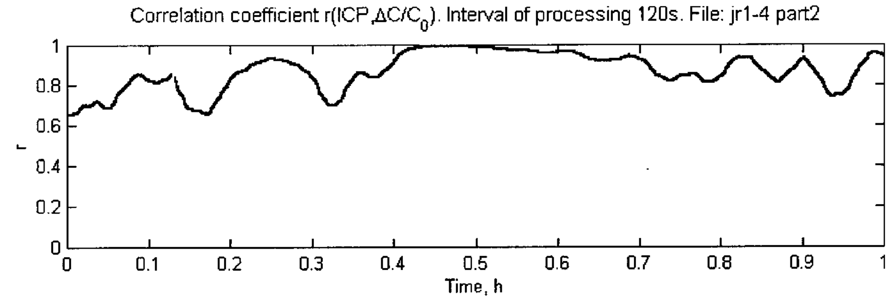


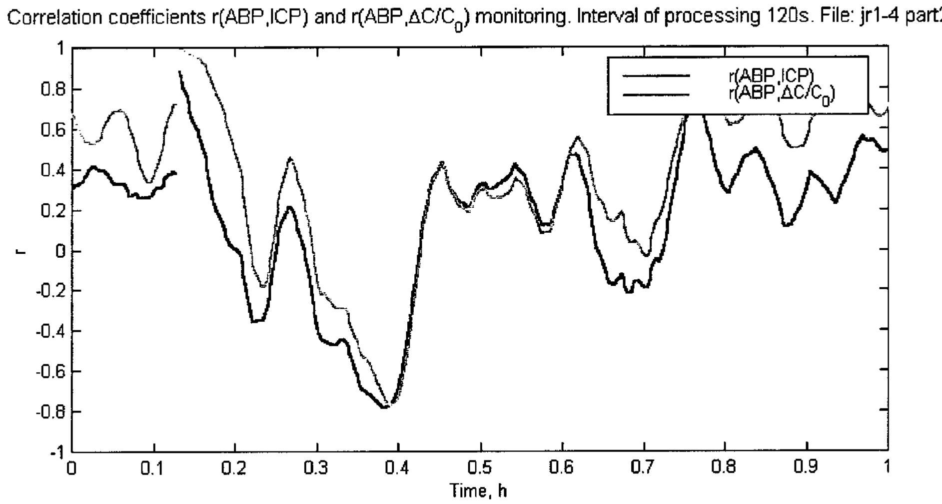
Statistical processing of r(ABP,ICP) and r(ABP,$\Delta C/C_0$): m=703, mD=-0.2139, S=0.1844, R=0.7936



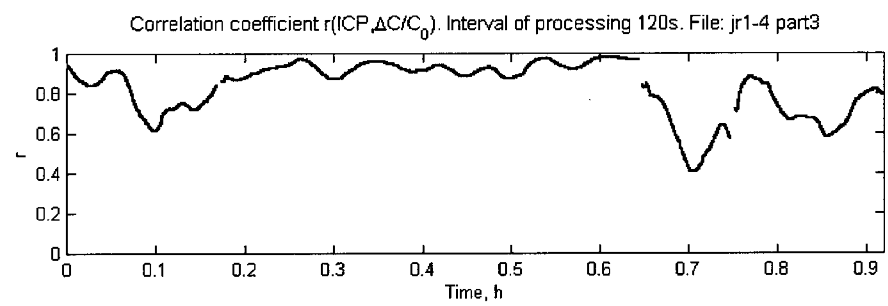


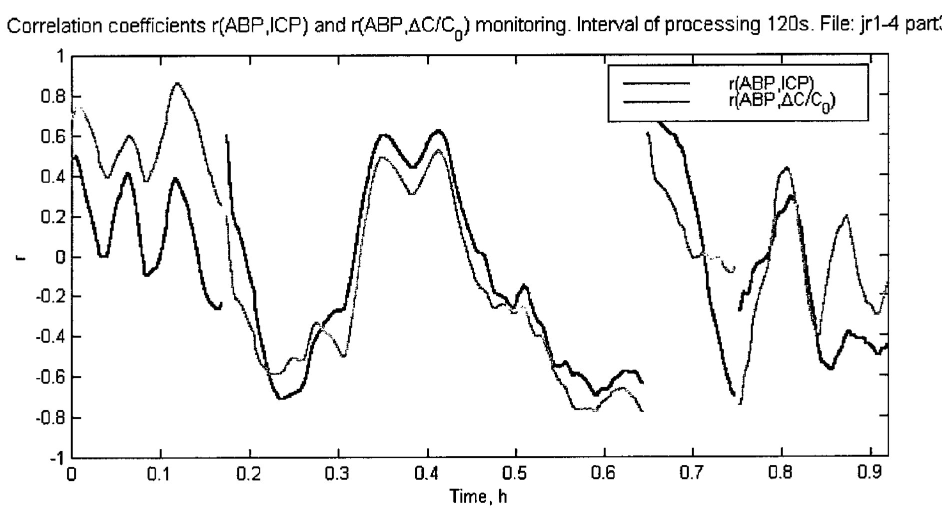
Statistical processing of r(ABP,ICP) and r(ABP,$\Delta C/C_0$): m=703, mD=-0.1066, S=0.1095, R=0.8842



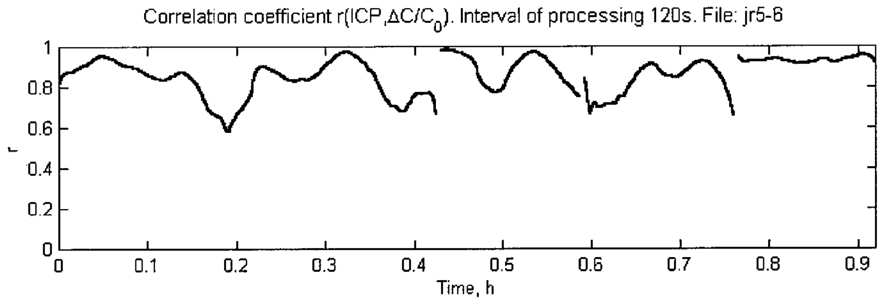


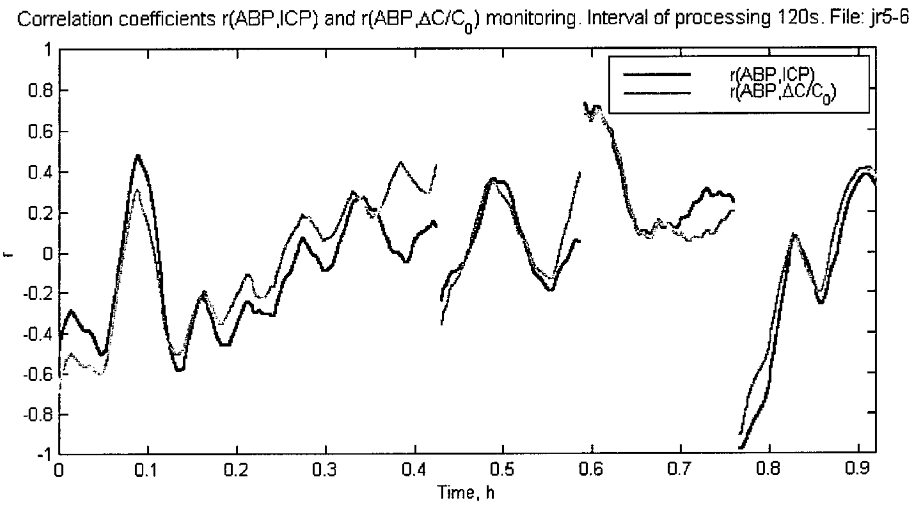
Statistical processing of r(ABP,ICP) and r(ABP,$\Delta C/C_0$): m=703, mD=-0.1942, S=0.1655, R=0.9149



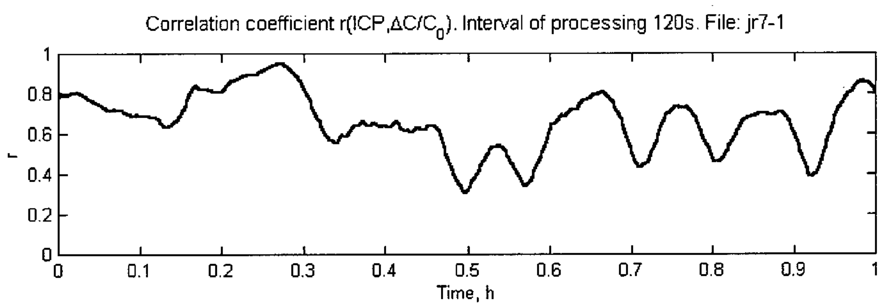


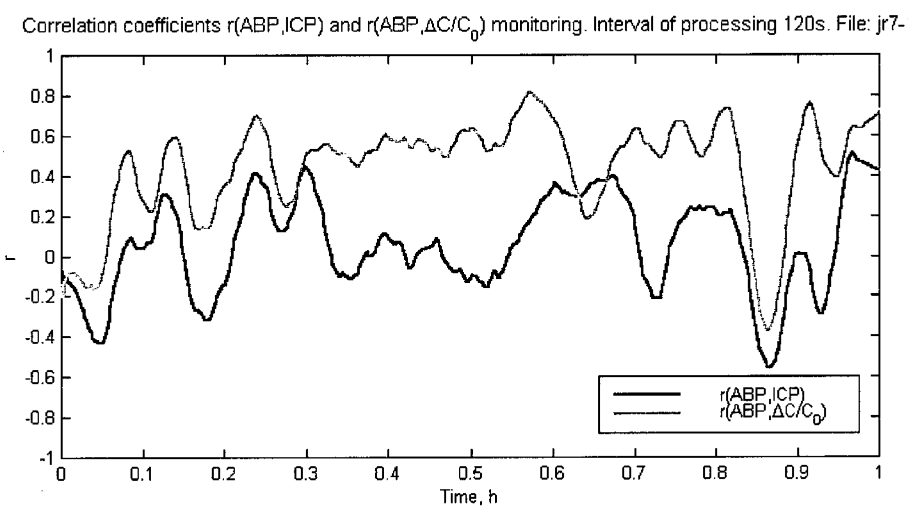
Statistical processing of r(ABP,ICP) and r(ABP,$\Delta C/C_0$): m=635, mD=-0.0481, S=0.2845, R=0.7881



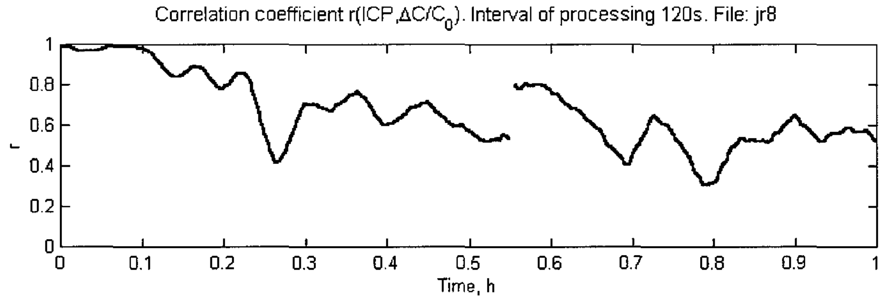


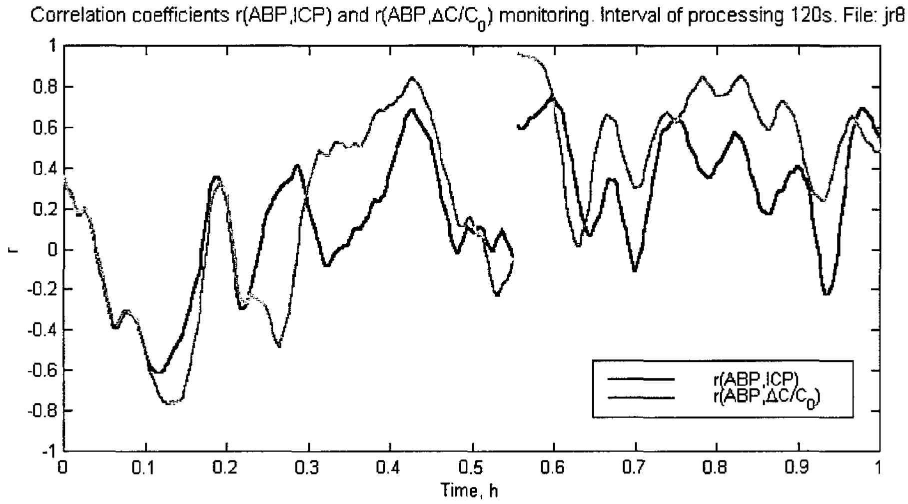
Statistical processing of r(ABP,ICP) and r(ABP,$\Delta C/C_0$): m=639, mD=-0.0347, S=0.1330, R=0.9144



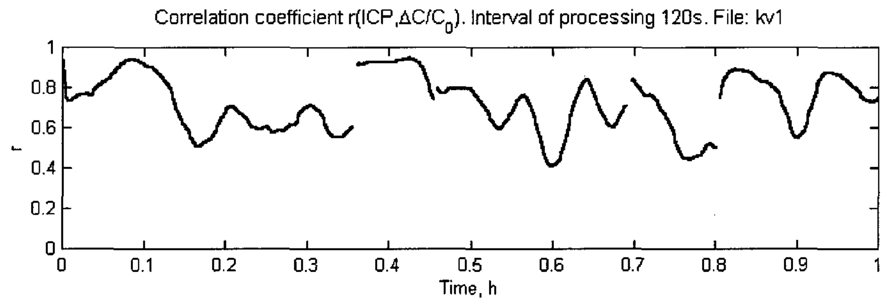


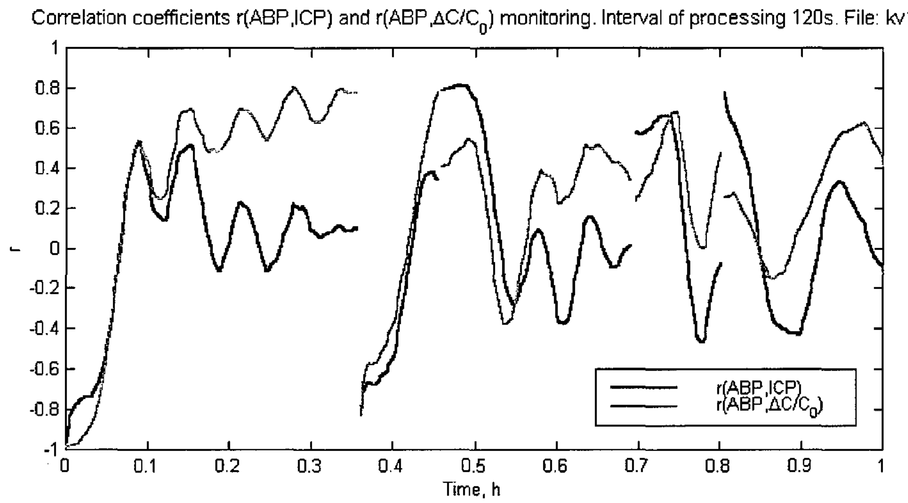
Statistical processing of r(ABP,ICP) and r(ABP,$\Delta C/C_0$): m=703, mD=-0.3873, S=0.2193, R=0.5988



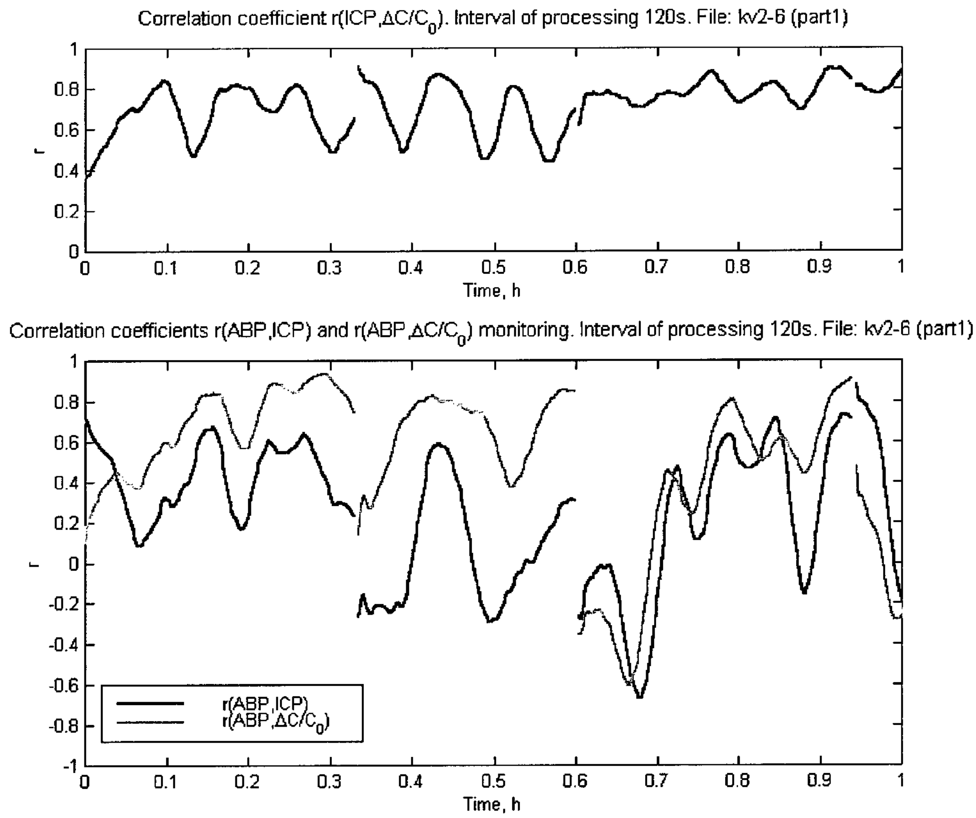


Statistical processing of r(ABP,ICP) and r(ABP,$\Delta C/C_0$): m=703, mD=-0.1050, S=0.2741, R=0.7933

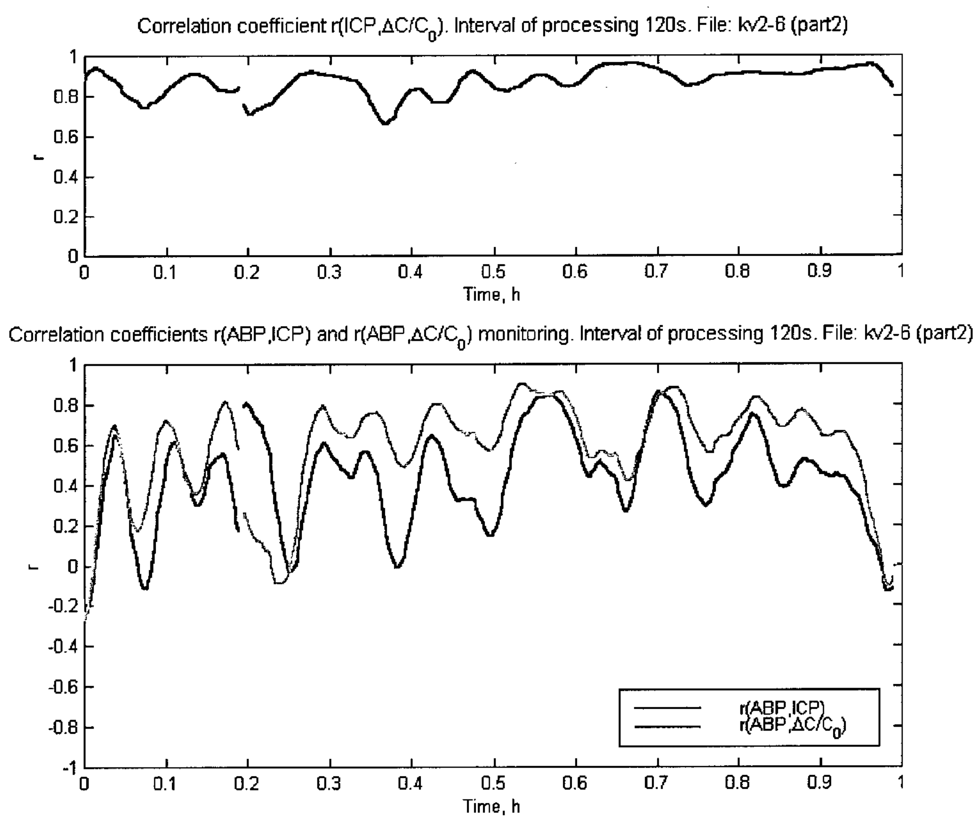




Statistical processing of r(ABP,ICP) and r(ABP,$\Delta C/C_0$): m=703, mD=-0.2228, S=0.3117, R=0.7074

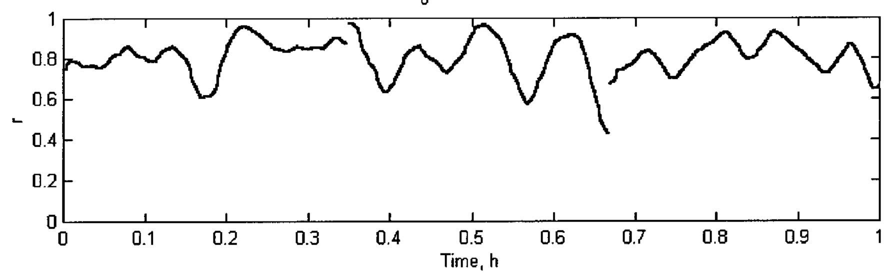


Statistical processing of r(ABP,ICP) and r(ABP,$\Delta C/C_0$): m=703, mD=-0.2577, S=0.3295, R=0.5645

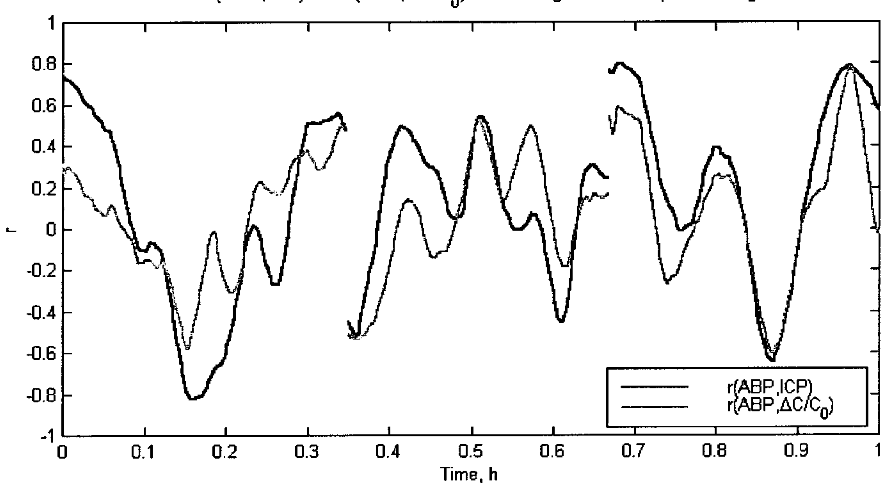


Statistical processing of r(ABP,ICP) and r(ABP,$\Delta C/C_0$): m=687, mD=-0.1464, S=0.2072, R=0.6049

Correlation coefficient r(ICP,ΔC/C$_0$). Interval of processing 120s. File: mm3-13

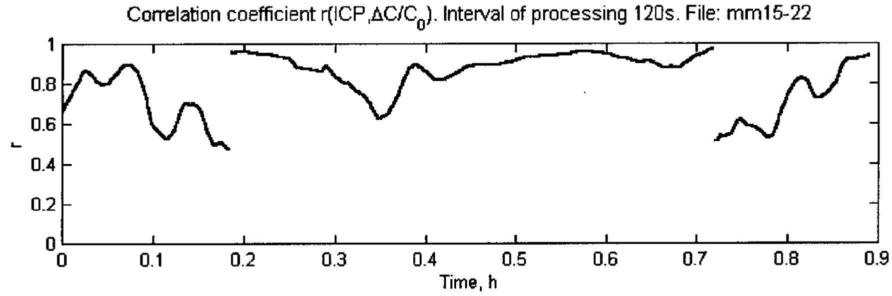


Correlation coefficients r(ABP,ICP) and r(ABP,ΔC/C$_0$) monitoring. Interval of processing 120s. File: mm3-13

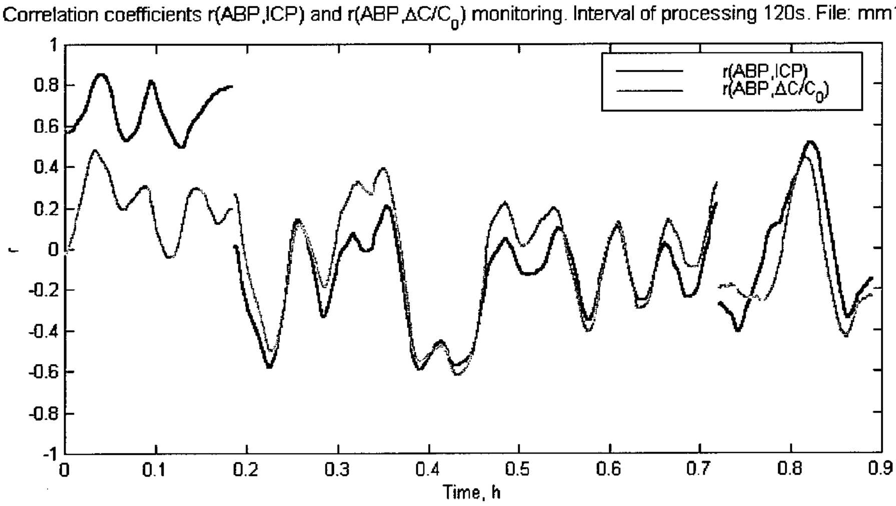


Statistical processing of r(ABP,ICP) and r(ABP,ΔC/C$_0$): m=703, mD=0.0676, S=0.2644, R=0.7806

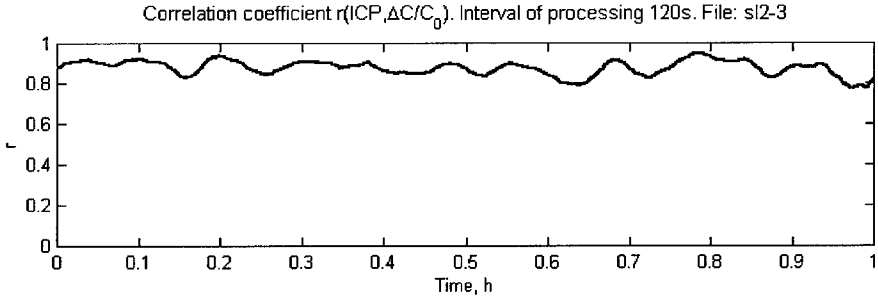
Correlation coefficient r(ICP,ΔC/C$_0$). Interval of processing 120s. File: mm15-22

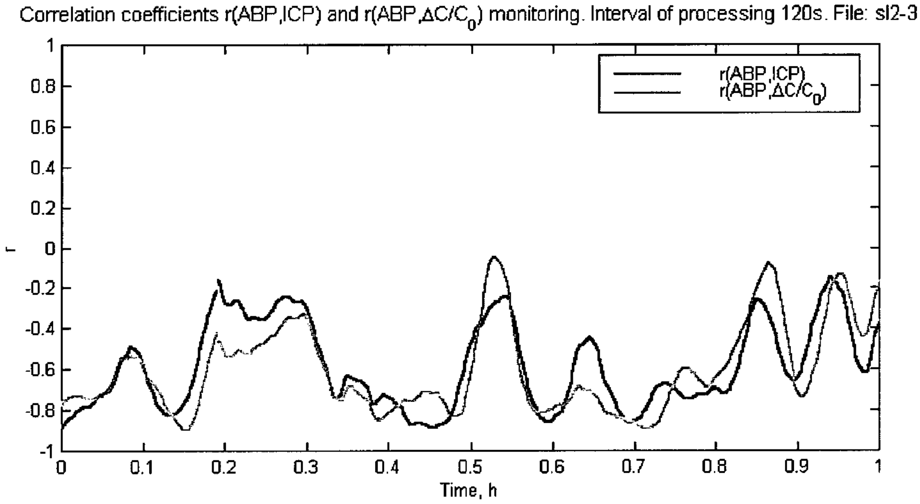


Correlation coefficients r(ABP,ICP) and r(ABP,ΔC/C$_0$) monitoring. Interval of processing 120s. File: mm15-22

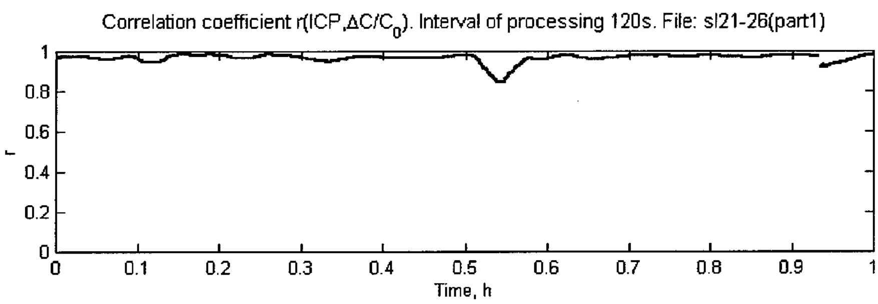


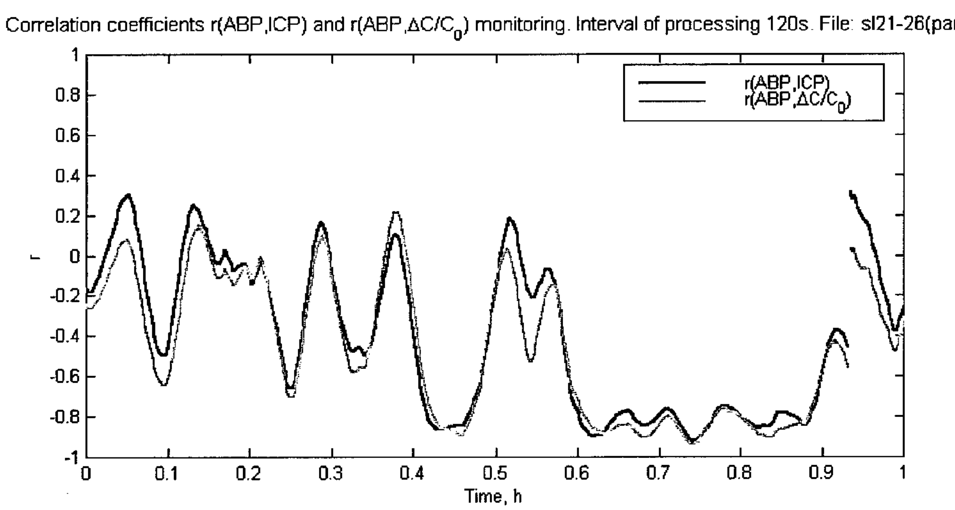
Statistical processing of r(ABP,ICP) and r(ABP,ΔC/C$_0$): m=623, mD=0.0620, S=0.2415, R=0.7967



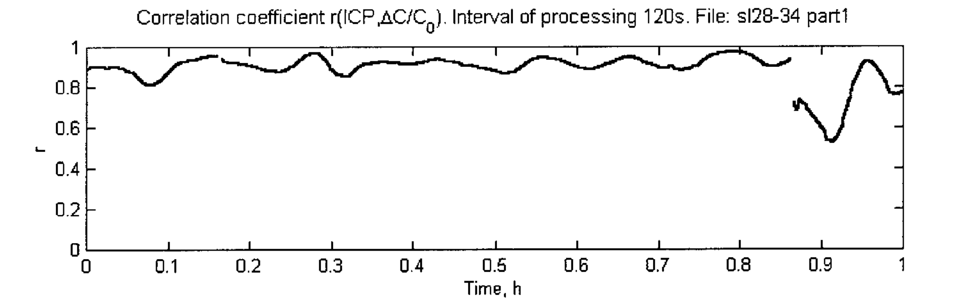


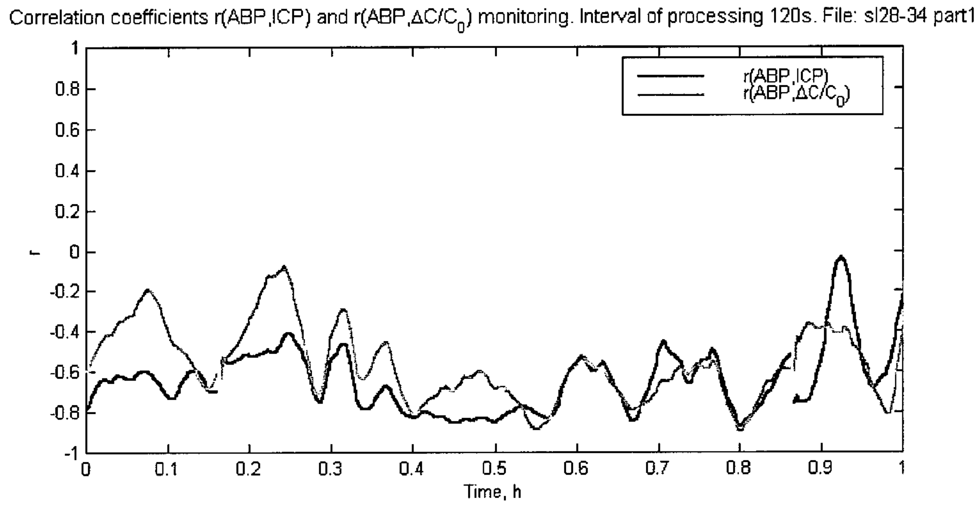
Statistical processing of r(ABP,ICP) and r(ABP,ΔC/C₀): m=703, mD=0.156, S=0.1302, R=0.8124



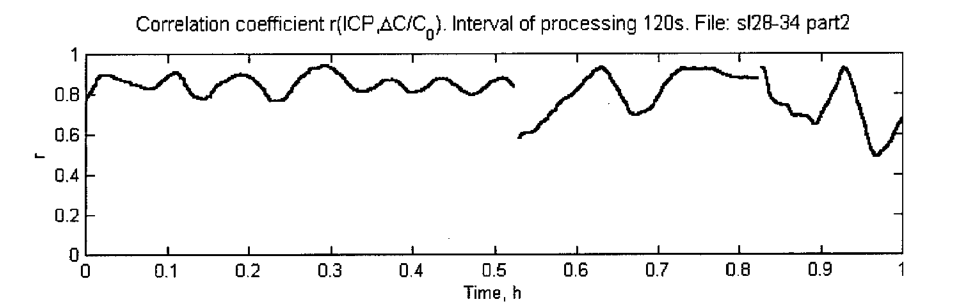


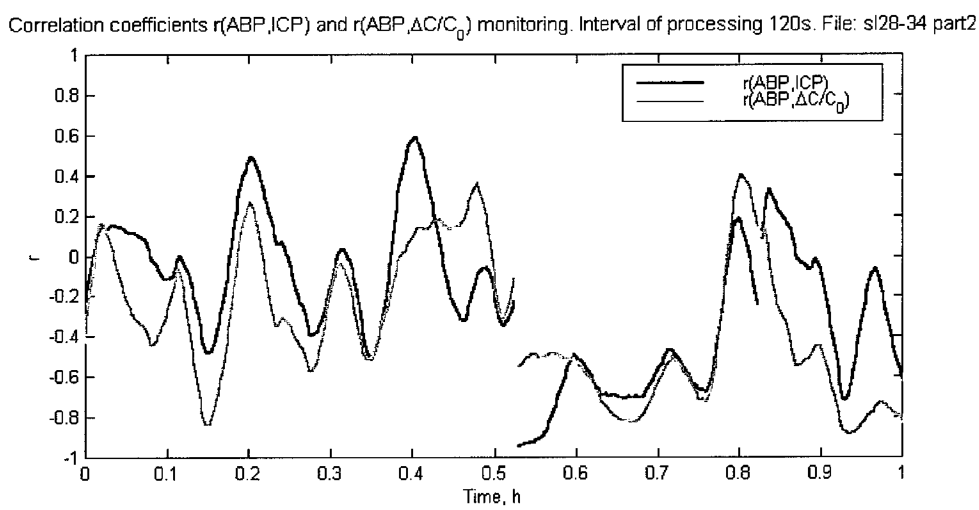
Statistical processing of r(ABP,ICP) and r(ABP,ΔC/C₀): m=703, mD=-0.0604, S=0.0945, R=0.9706



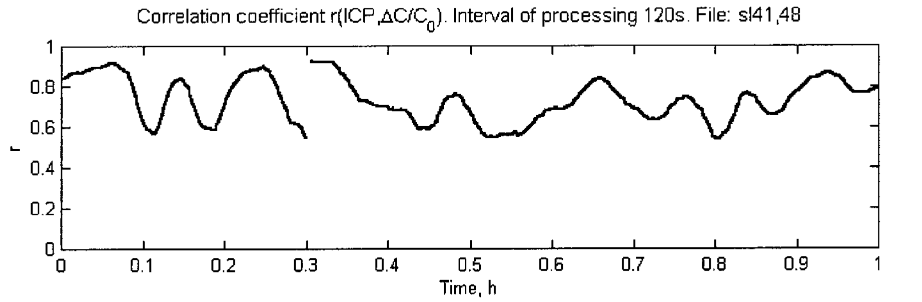


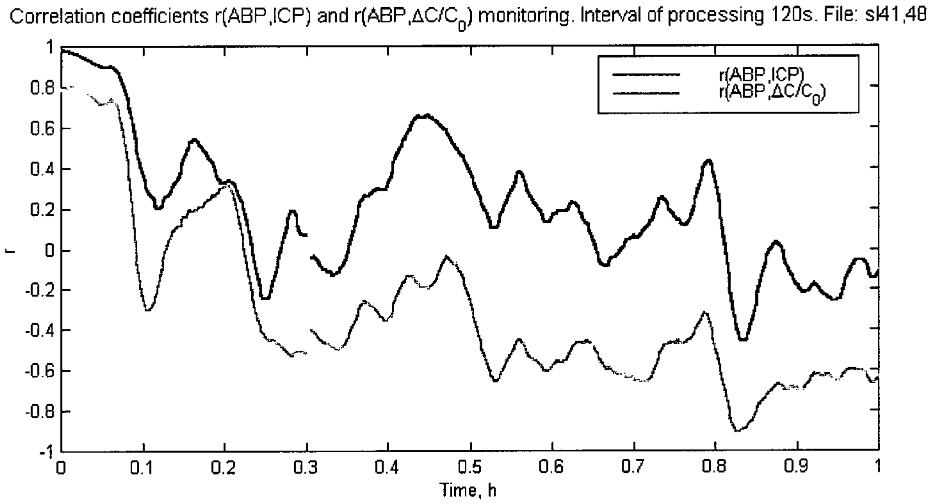
Statistical processing of r(ABP,ICP) and r(ABP,$\Delta C/C_0$): m=703, mD=-0.0792, S=0.1564, R=0.5975



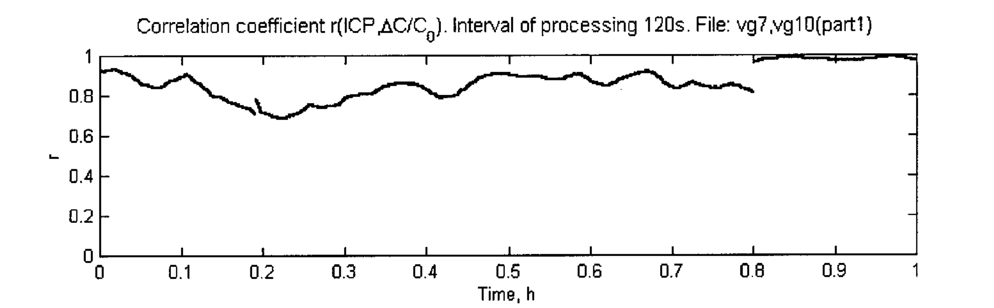


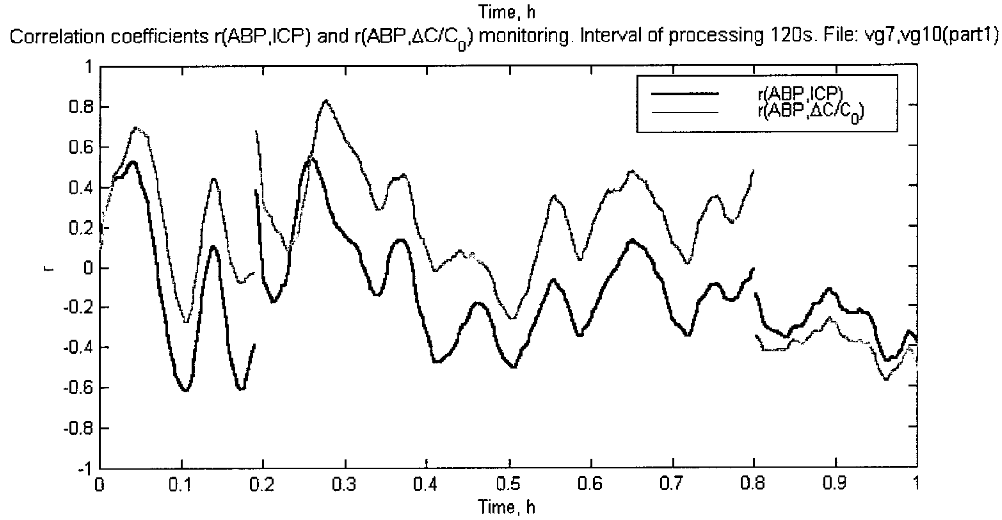
Statistical processing of r(ABP,ICP) and r(ABP,$\Delta C/C_0$): m=697, mD=-0.1268, S=0.02646, R=0.7174





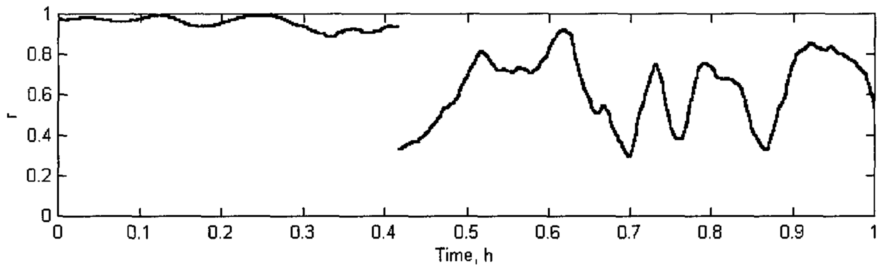
Statistical processing of r(ABP,ICP) and r(ABP,$\Delta C/C_0$): m=703, mD=0.5204, S=0.2130, R=0.8618



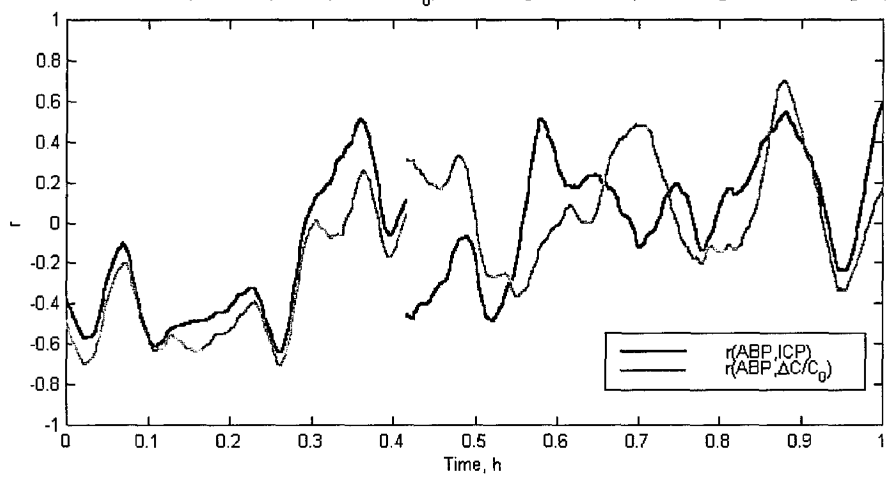


Statistical processing of r(ABP,ICP) and r(ABP,$\Delta C/C_0$): m=703, mD=-0.2493, S=0.2195, R=0.7674

Correlation coefficient r(ICP,ΔC/C0). Interval of processing 120s. Files: vg10(part2),vg2

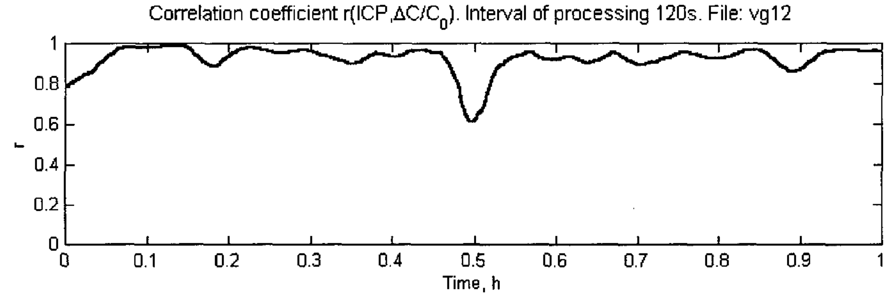


Correlation coefficients r(ABP,ICP) and r(ABP,ΔC/C0) monitoring. Interval of processing 120s. Files: vg10(part2),vg2

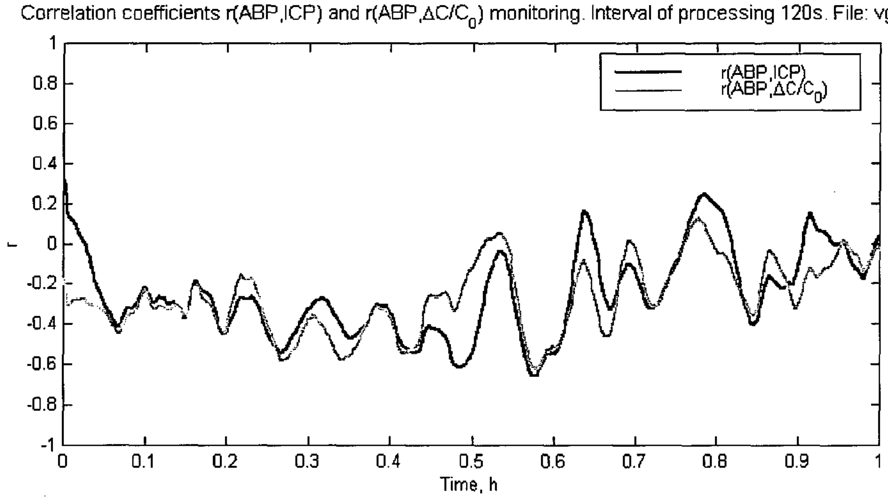


Statistical processing of r(ABP,ICP) and r(ABP,ΔC/C$_0$): m=703, mD=0.0400, S=0.2612, R=0.7057

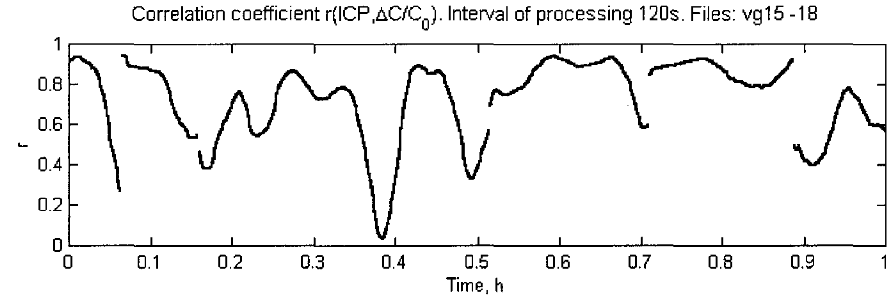
Correlation coefficient r(ICP,ΔC/C0). Interval of processing 120s. File: vg12

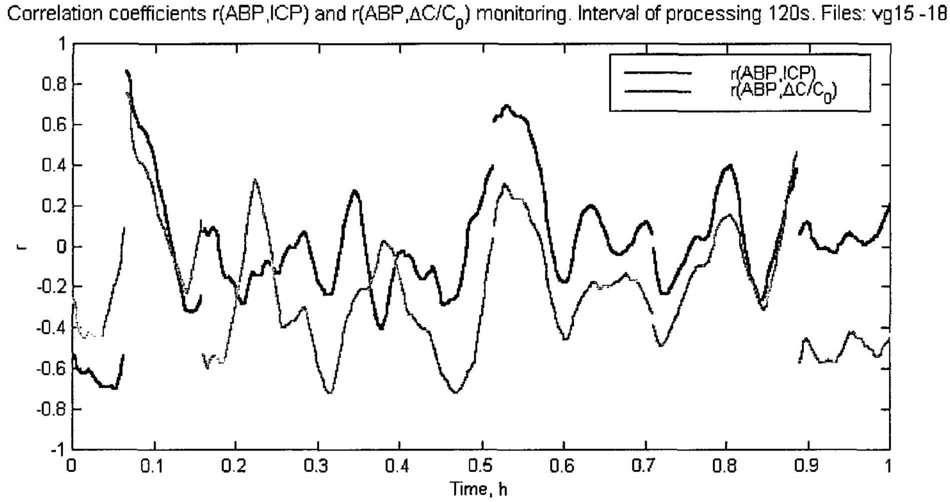


Correlation coefficients r(ABP,ICP) and r(ABP,ΔC/C0) monitoring. Interval of processing 120s. File: vg12

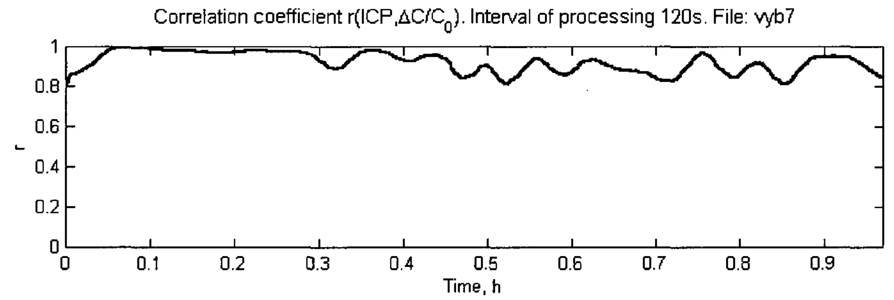


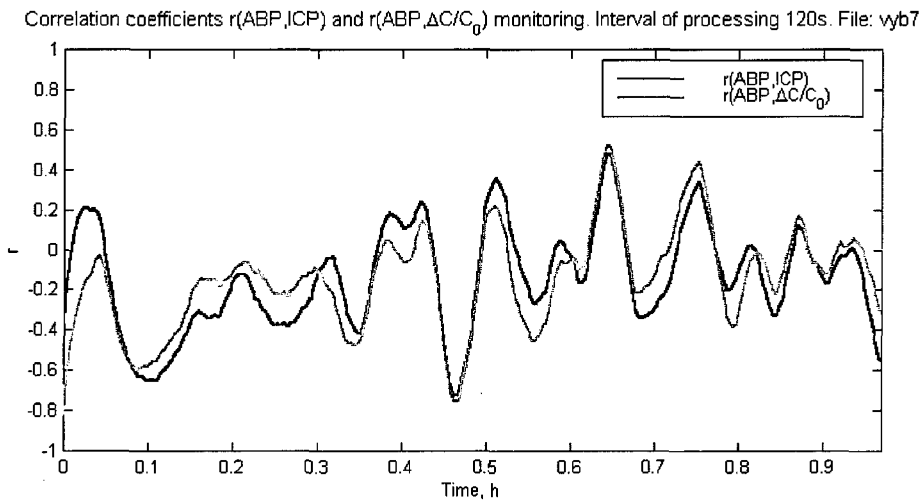
Statistical processing of r(ABP,ICP) and r(ABP,ΔC/C$_0$): m=703, mD=0.0180, S=0.1435, R=0.7428



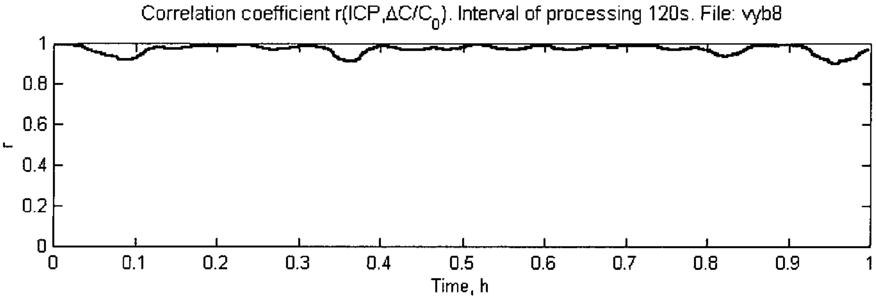


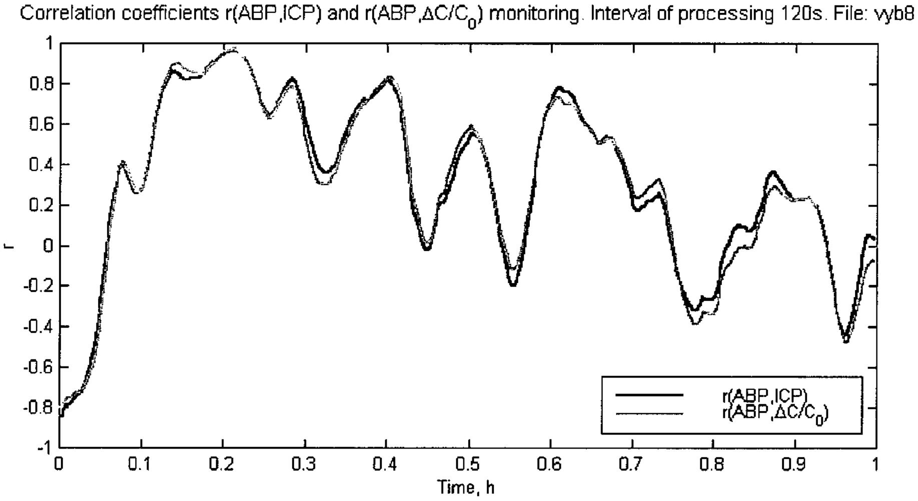
Statistical processing of r(ABP,ICP) and r(ABP,$\Delta C/C_0$): m=703, mD=0.2259, S=0.2821, R=0.5355



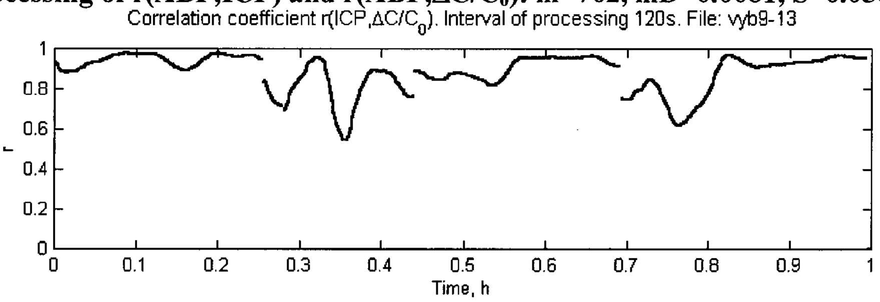


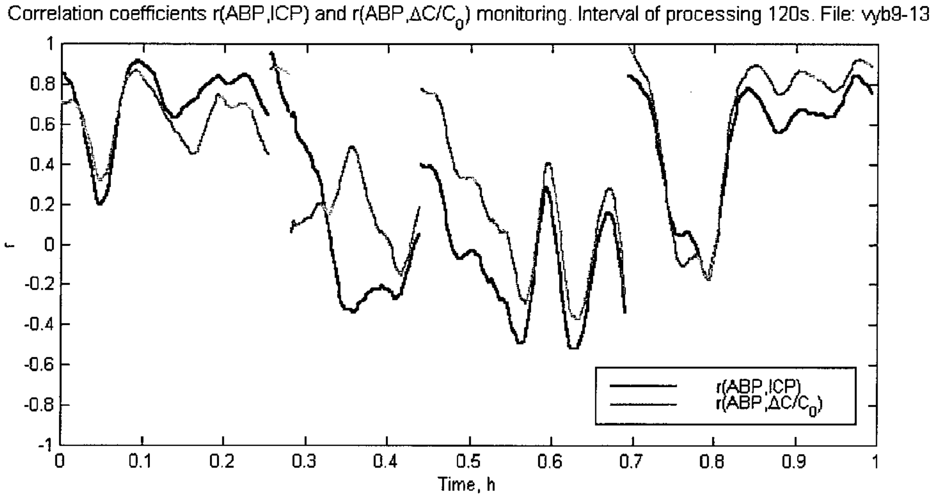
Statistical processing of r(ABP,ICP) and r(ABP,$\Delta C/C_0$): m=682, mD=0.0029, S=0.1433, R=0.8404



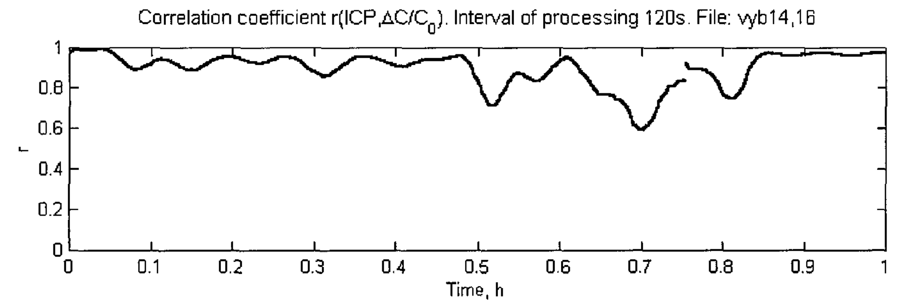


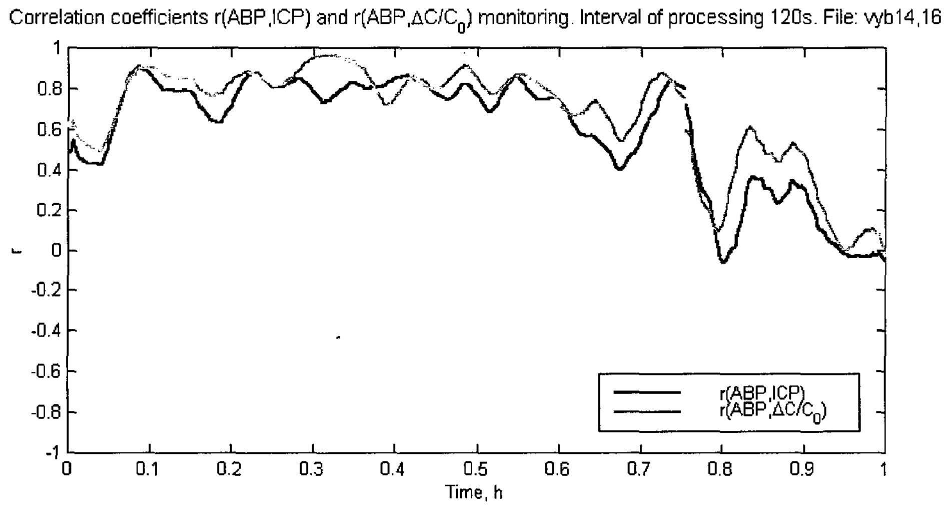
Statistical processing of r(ABP,ICP) and r(ABP,$\Delta C/C_0$): m=702, mD=0.0081, S=0.0504, R=0.9932



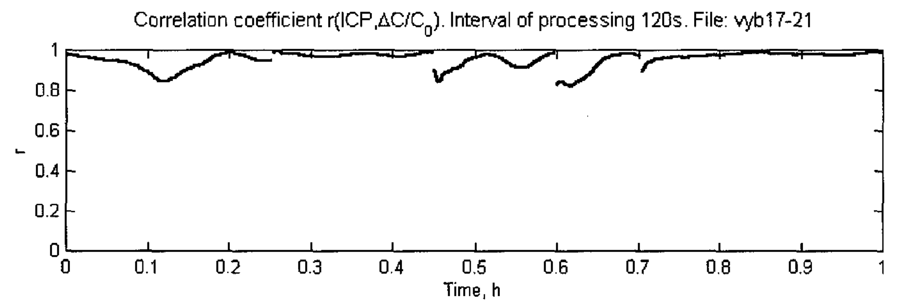


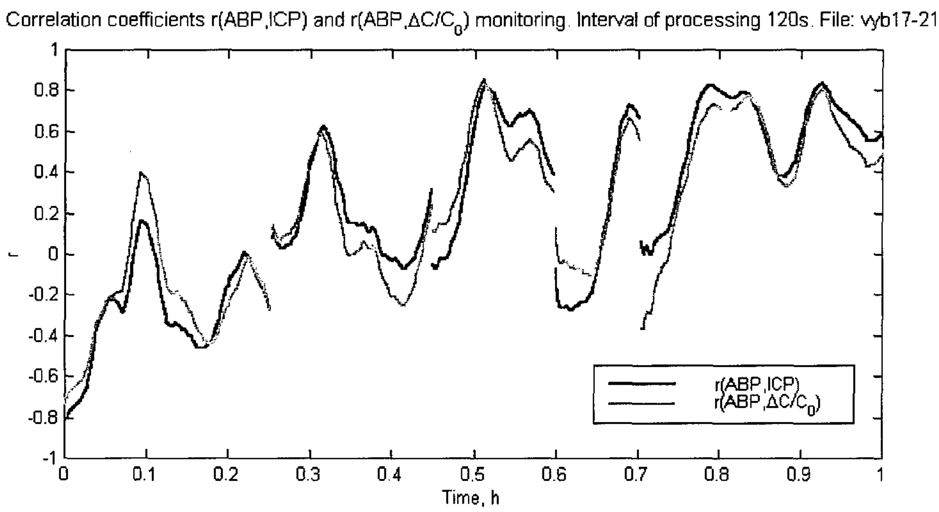
Statistical processing of r(ABP,ICP) and r(ABP,$\Delta C/C_0$): m=696, mD=-0.0966, S=0.2122, R=0.8652





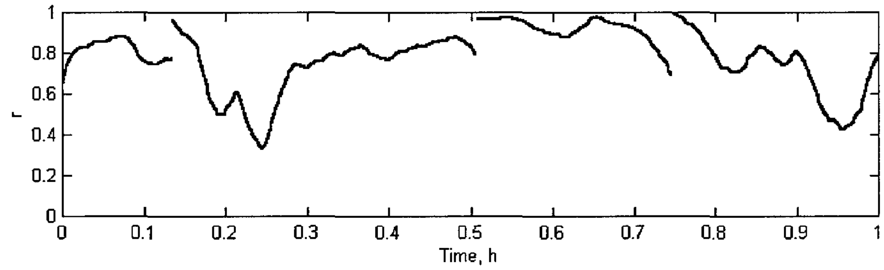
Statistical processing of r(ABP,ICP) and r(ABP,ΔC/C$_0$): m=703, mD=-0.0808, S=0.0871, R=0.9521



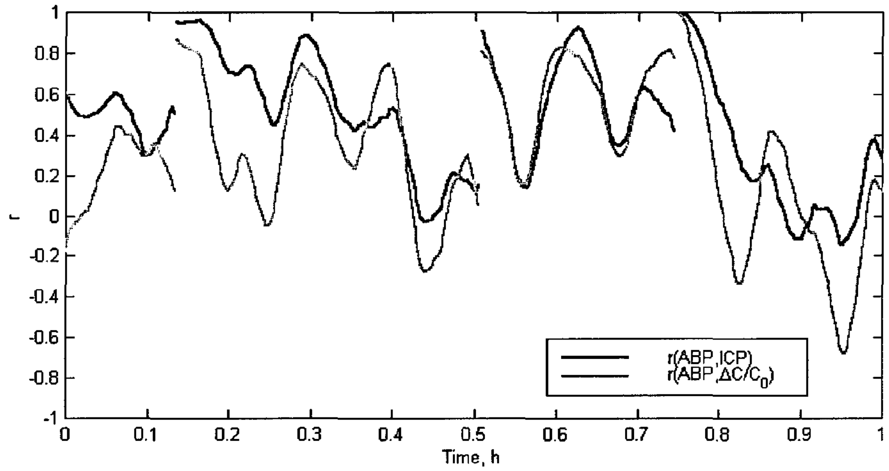


Statistical processing of r(ABP,ICP) and r(ABP,ΔC/C$_0$): m=703, mD=0.0112, S=0.1271, R=0.9541

Correlation coefficient r(ICP,ΔC/C$_0$). Interval of processing 120s. File: vyb1-3

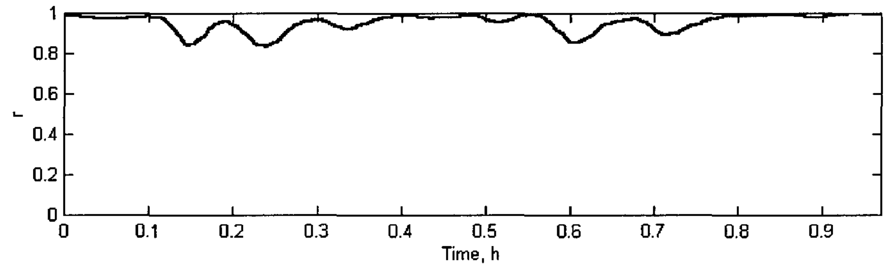


Correlation coefficients r(ABP,ICP) and r(ABP,ΔC/C$_0$) monitoring. Interval of processing 120s. File: vyb1-3

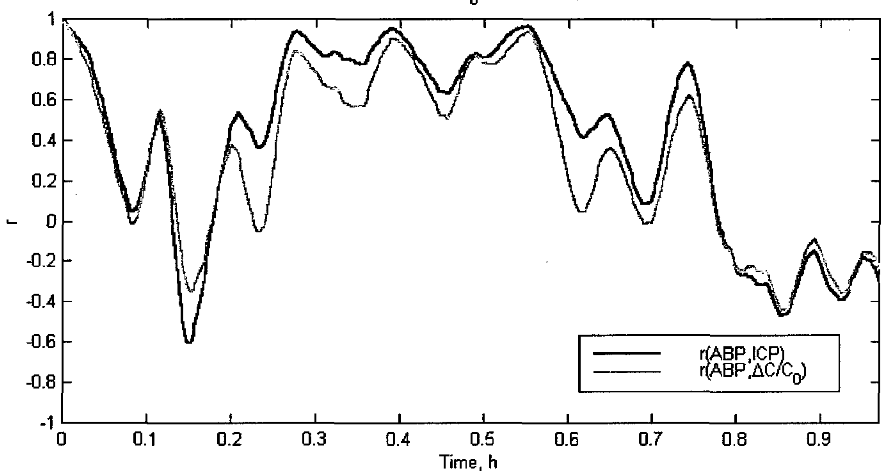


Statistical processing of r(ABP,ICP) and r(ABP,ΔC/C$_0$): m=703, mD=0.1469, S=0.2335, R=0.7649

Correlation coefficient r(ICP,ΔC/C$_0$). Interval of processing 120s. File: vyb6

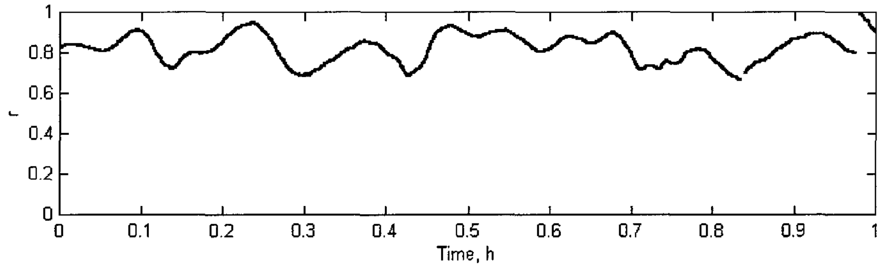


Correlation coefficients r(ABP,ICP) and r(ABP,ΔC/C$_0$) monitoring. Interval of processing 120s. File: vyb6

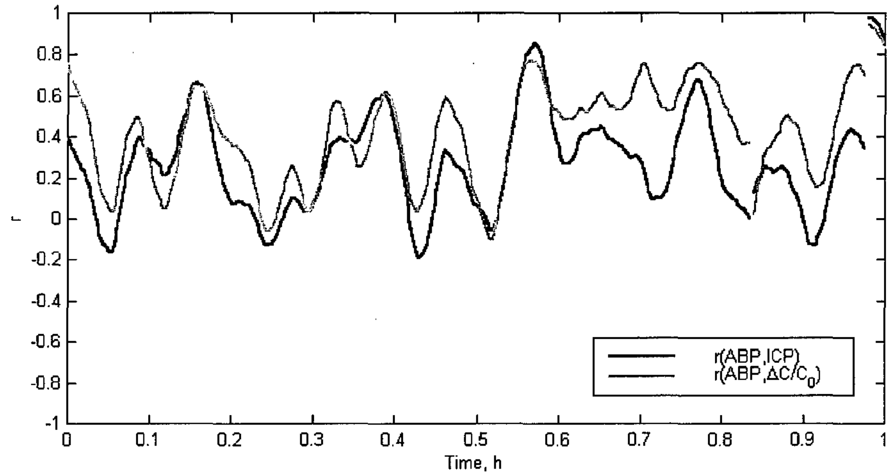


Statistical processing of r(ABP,ICP) and r(ABP,ΔC/C$_0$): m=684, mD=0.0747, S=0.1281, R=0.9639

Correlation coefficient r(ICP,ΔC/C0). Interval of processing 120s. File: vk1-3

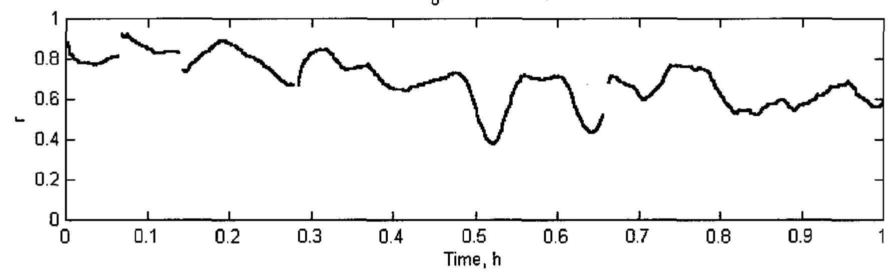


Correlation coefficients r(ABP,ICP) and r(ABP,ΔC/C0) monitoring. Interval of processing 120s. File: vk1-3

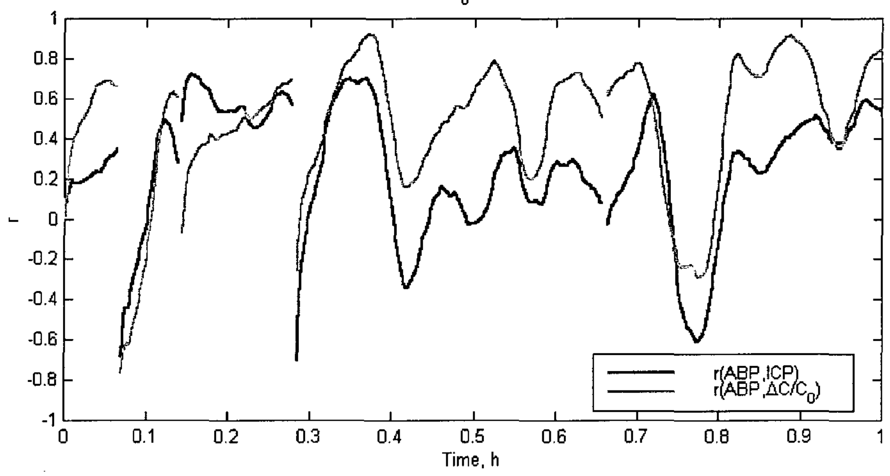


Statistical processing of r(ABP,ICP) and r(ABP,ΔC/C$_0$): m=703, mD=-0.1468, S=0.1546, R=0.7954

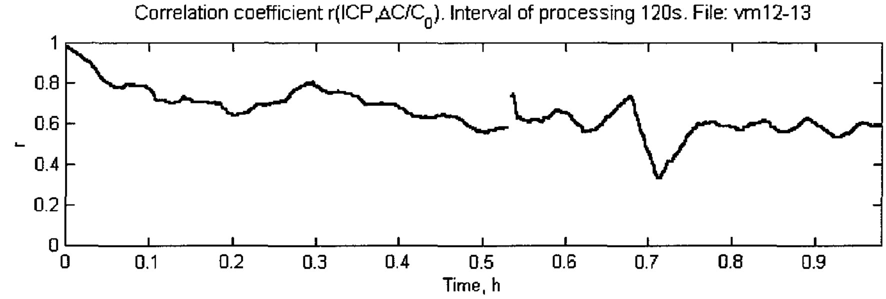
Correlation coefficient r(ICP,ΔC/C0). Interval of processing 120s. File: vm5-10

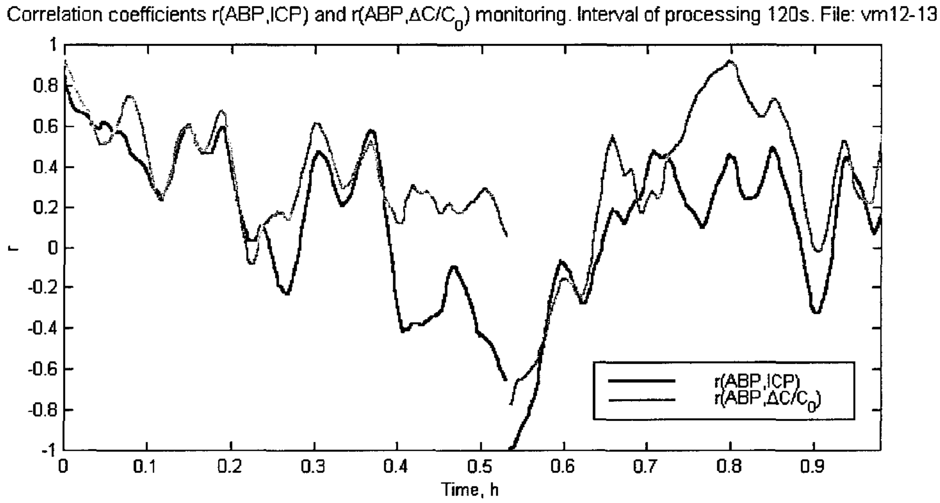


Correlation coefficients r(ABP,ICP) and r(ABP,ΔC/C0) monitoring. Interval of processing 120s. File: vm5-10

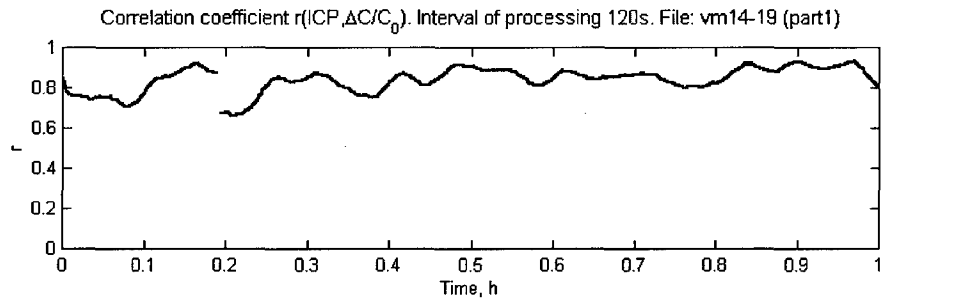


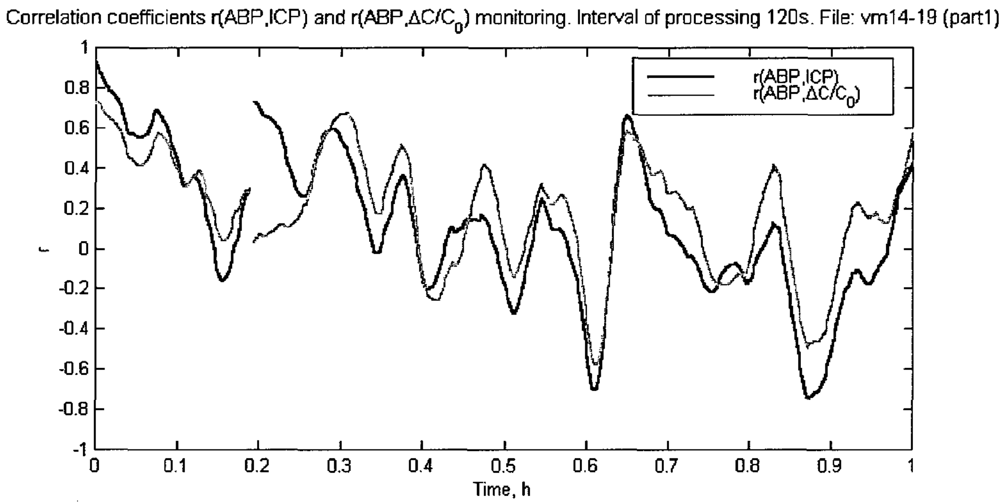
Statistical processing of r(ABP,ICP) and r(ABP,ΔC/C$_0$): m=703, mD=-0.2288, S=0.2500, R=0.6953





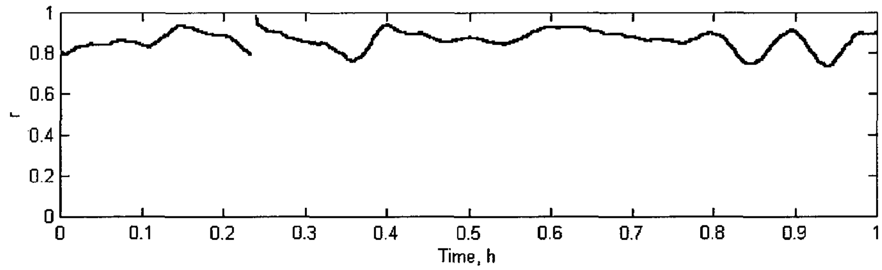
Statistical processing of r(ABP,ICP) and r(ABP,ΔC/C₀): m=692, mD=-0.2109, S=0.2332, R=0.7893



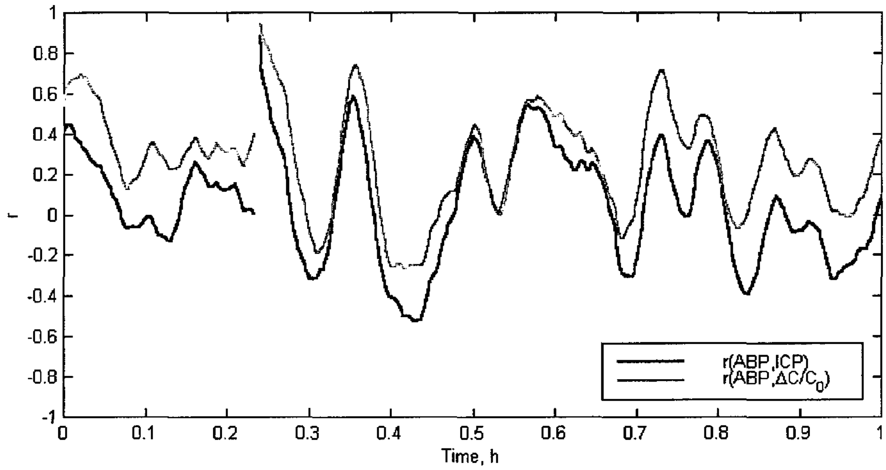


Statistical processing of r(ABP,ICP) and r(ABP,ΔC/C_0): m=703, mD=-0.00670, S=0.1897, R=0.8495

Correlation coefficient r(ICP,ΔC/C_0). Interval of processing 120s. File: vm14-19 (part2)

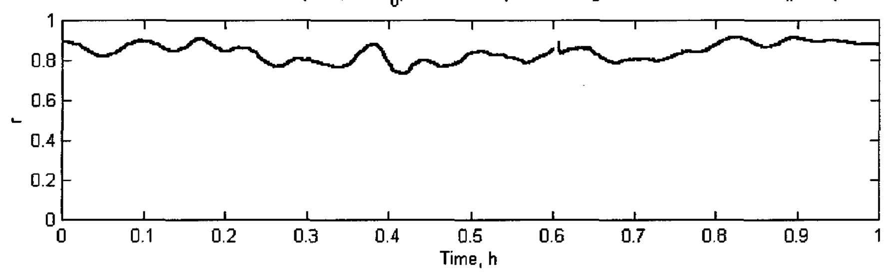


Correlation coefficients r(ABP,ICP) and r(ABP,ΔC/C_0) monitoring. Interval of processing 120s. File: vm14-19 (part2)

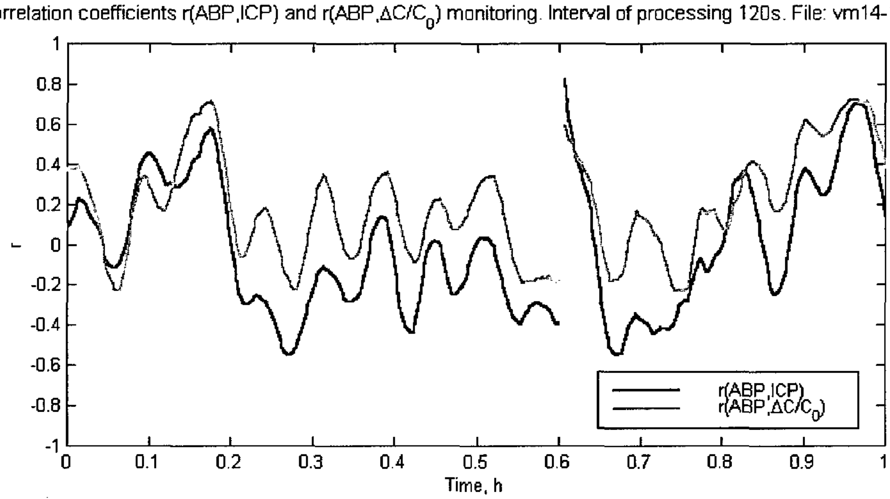


Statistical processing of r(ABP,ICP) and r(ABP,ΔC/C_0): m=703, mD=-0.2166, S=0.1136, R=0.9071

Correlation coefficient r(ICP,ΔC/C_0). Interval of processing 120s. File: vm14-19 (part3)

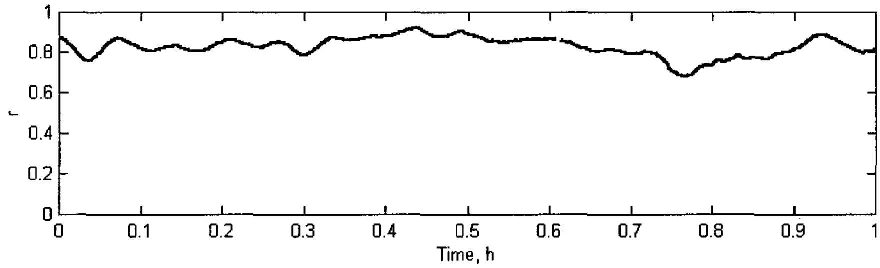


Correlation coefficients r(ABP,ICP) and r(ABP,ΔC/C_0) monitoring. Interval of processing 120s. File: vm14-19 (part3)

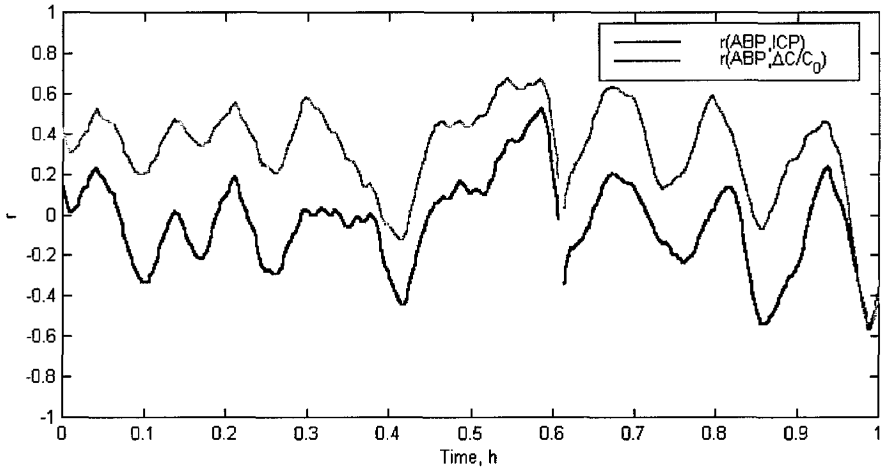


Statistical processing of r(ABP,ICP) and r(ABP,ΔC/C_0): m=703, mD=-0.2107, S=0.1627, R=0.8693

Correlation coefficient $r(ICP,\Delta C/C_0)$. Interval of processing 120s. File: vm14-19 (part4)

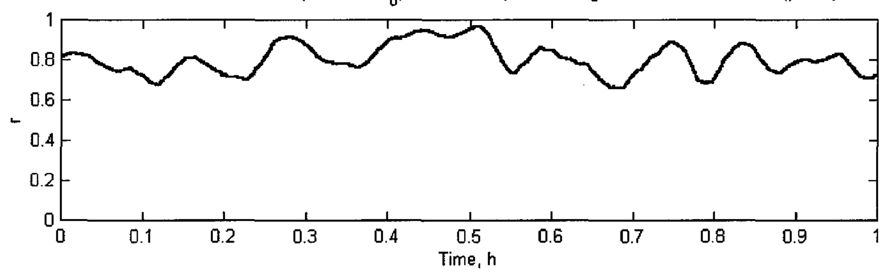


Correlation coefficients $r(ABP,ICP)$ and $r(ABP,\Delta C/C_0)$ monitoring. Interval of processing 120s. File: vm14-19 (part4)

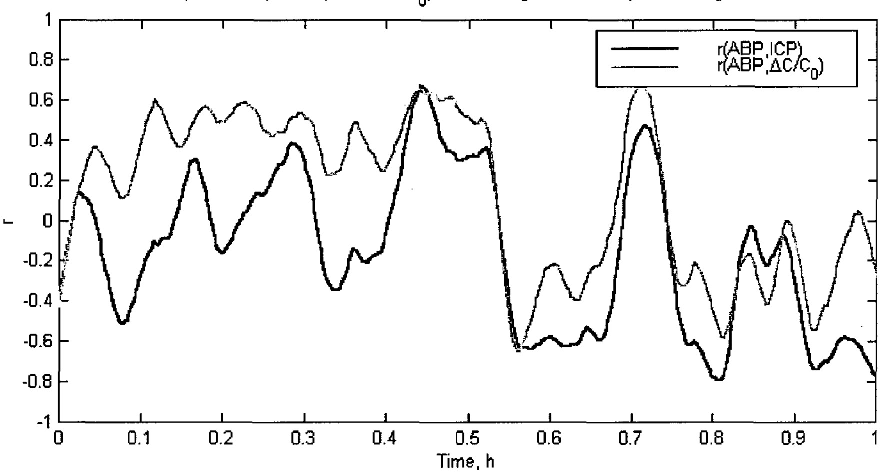


Statistical processing of r(ABP,ICP) and r(ABP,ΔC/C$_0$): m=703, mD=-0.3641, S=0.1406, R=0.8157

Correlation coefficient $r(ICP,\Delta C/C_0)$. Interval of processing 120s. File: vm14-19 (part5)

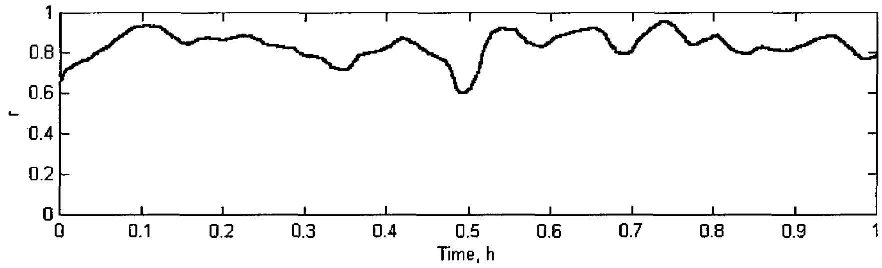


Correlation coefficients $r(ABP,ICP)$ and $r(ABP,\Delta C/C_0)$ monitoring. Interval of processing 120s. File: vm14-19 (part5)

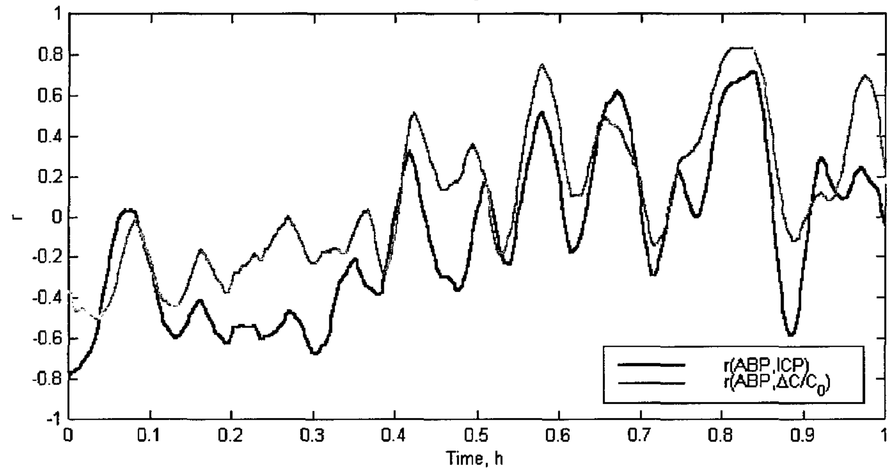


Statistical processing of r(ABP,ICP) and r(ABP,ΔC/C$_0$): m=703, mD=-0.2963, S=0.2215, R=0.8380

Correlation coefficient r(ICP,ΔC/C_0). Interval of processing 120s. File: vm20



Correlation coefficients r(ABP,ICP) and r(ABP,ΔC/C_0) monitoring. Interval of processing 120s. File: vm20



Statistical processing of r(ABP,ICP) and r(ABP,ΔC/C_0): m=703, mD=-0.1978, S=0.1910, R=0.8709

APPENDIX D

ATACCC 2001, Fort Walton Beach (ABSTRACT OF ORAL PRESENTATION)

A. RAGAUSKAS

NON-INVASIVE MEASUREMENT OF INTRACRANIAL PRESSURE (ICP)

Objective: New ultrasonographic non-invasive ICP / Volume monitoring and ICP absolute value measurement methods were proposed in our previous works [1,2]. The objective of this paper is to present our clinical results of the assessment of non-invasive technology for cerebrovascular autoregulation monitoring and non-invasive ICP absolute value measurement in the intensive care unit (ICU).
Methods: Slow intracranial wave and ABP slow wave correlation methodology was used for cerebrovascular autoregulation monitoring. Non-invasive cerebrovascular slow wave monitor (Vittamed) has been used together with invasive ICP and ABP slow wave monitors in the ICU. Also ultrasonographic absolute ICP meter (Vittamed) was applied for periodic non-invasive measurements of ICU patients with traumatic brain injuries. All measurements were performed following Clinical Research Protocol of DoD Agreement DAMD 17-00-2-0065.
The non-invasively recorded slow volumetric intracranial waves were compared with invasively recorded slow ICP waves. Also continuous monitoring of the correlation factor R_I between invasively recorded ICP and ABP slow waves was performed simultaneously with non-invasively recorded correlation factor R_N between volumetric slow waves and ABP slow waves. The accuracy of absolute ICP non-invasive measurement was evaluated comparing non-invasive ICP data with simultaneously invasively measured ICP values.
Results: It has been shown experimentally that the correlation factor between invasively and non-invasively recorded slow ICP waves is not less than 0.71...0.93 during one hour monitoring periods (15 one hour ICU monitoring periods were analyzed). It has been shown an excellent agreement between non-invasive and invasive cerebrovascular autoregulation monitoring data.
The preliminary results of non-invasive ICP measurement method clinical assessment show that this is only method for non-invasive ICP measurement without the problem of individual calibration of system "patient – non-invasive ICP meter".
Conclusion: In this ongoing study it is shown at the first time that non-invasive ultrasonographic time-of-flight technology could be applied for continuous cerebrovascular autoregulation monitoring. It is shown that non-invasive absolute ICP meter (Vittamed) is only non-invasive ICP meter, which does not need an individual calibration of system "patient – non-invasive ICP meter".

1. Cerebrovasc Dis 1999;9 (suppl.2):31 and 46, also 2000;10 (suppl.1):34.
2. US Patents 5, 388, 583 and 5, 951, 477.

ATACCC 2002, Fort Sant Pete Beach (ABSTRACT OF ORAL PRESENTATION)

A. RAGAUSKAS

COMPARATIVE CLINICAL STUDY OF INVASIVE AND NON-INVASIVE INTRACRANIAL PRESSURE MONITORING TECHNIQUES

Objective: New ultrasonographic non-invasive intracranial pressure (ICP) / intracranial blood volume (IBV) monitoring and ICP absolute value measurement methods were proposed in our previous works [1,2]. The objective of this paper is to present the results of the completed comparative clinical study of invasive and non-invasive technology for cerebrovascular autoregulation monitoring and also invasive and non-invasive ICP absolute value measurement

in the neurosurgical intensive care unit (ICU).
Methods: In order to obtain a required statistical power of conclusions the number of patients was determined 10 and the number of measurement cycles was determined N>52 for this study. We performed 87 sessions of one hour simultaneous ICP and IBV wave monitoring on 12 ICU patients with severe traumatic brain injuries. We also performed 53 sessions of one hour simultaneous invasive and non-invasive cerebrovascular autoregulation monitoring on 10 patients from the same group. Invasive and non-invasive absolute ICP measurements (N=54) also have been performed on 10 ICU patients.

Slow ICP wave and slow ABP wave correlation methodology was used for invasive cerebrovascular autoregulation monitoring. Non-invasive IBV slow wave monitor (Vittamed) has been used together with invasive ICP and ABP slow wave monitors for simultaneous monitoring in the ICU. Also ultrasonographic absolute ICP meter (Vittamed) was applied for periodic non-invasive measurements on ICU patients with traumatic brain injuries. All measurements were performed following Clinical Research Protocol No. 9912 4006 (HSRRB Log No. A-9676) of DoD Agreement DAMD 17-00-2-0065.

The non-invasively recorded slow IBV waves were compared with simultaneously invasively recorded slow ICP waves. Also continuous monitoring of the correlation factor R_I between invasively recorded ICP and ABP slow waves was performed simultaneously with non-invasively recorded correlation factor R_N between IBV and ABP slow waves.

Statistical analysis (Student's *t*-test, Bland Altman plot, correlation analysis, etc.) of invasively and non-invasively measured data has been performed in order to evaluate a coincidence of invasively and non-invasively measured results.

Results: It has been shown experimentally that the reliable short- or long-term continuous non-invasive cerebrovascular autoregulation monitoring (Vittamed) can be used under ICU conditions. Statistically significant estimation (12 patients) shows that the hypothesis of the coincidence of invasively and non-invasively measured ICP and IBV slow wave data is accepted (π>0.95). Statistically estimated (Bland Altman) difference between invasively and non-invasively recorded intracranial slow waves (SD=0.089, $p=4.5\times10^{-7}$) and the difference between invasively and non-invasively recorded cerebral autoregulation indexes (SD=0.05, $p=1.1\times10^{-6}$) is small enough and such differences are not clinically important.

Bland Altman plot of 52 invasive and non-invasive measurements (10 patients) of absolute ICP values shows that the proposed method of non-invasive absolute ICP measurement (Vittamed) is only the method which does not need an individual calibration of the system "patient – non-invasive ICP meter". A good agreement was obtained between experimental results and mathematical modeling results of non-invasive absolute ICP measurement.

Conclusion: In this completed clinical study the statistically significant evidences were obtained at the first time that ultrasonographic time-of-flight technology (Vittamed) could be applied for non-invasive continuous cerebrovascular autoregulation monitoring. It is also evident that non-invasive absolute ICP meter (Vittamed) is only non-invasive ICP meter which does not need an individual calibration of system "patient – non-invasive ICP meter".

1. Cerebrovasc Dis 1999;9 (S2):31 and 46, Cerebrovasc Dis 2000;10 (S1):34, Cerebrovasc Dis 2002;13 (S4):18 and 25.
2. US Patents No. 5, 388, 583, No. 5, 951, 477, No. 6, 387, 051.

DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

REPLY TO
ATTENTION OF:

MCMR-RMI-S (70-1y) 18 Apr 03

MEMORANDUM FOR Administrator, Defense Technical Information Center (DTIC-OCA), 8725 John J. Kingman Road, Fort Belvoir, VA 22060-6218

SUBJECT: Request Change in Distribution Statement

1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to technical reports written for this Command. Request the limited distribution statement for the enclosed accession numbers be changed to "Approved for public release; distribution unlimited." These reports should be released to the National Technical Information Service.

2. Point of contact for this request is Ms. Kristin Morrow at DSN 343-7327 or by e-mail at Kristin.Morrow@det.amedd.army.mil.

FOR THE COMMANDER:

Phyllis Rinehart

Encl

PHYLLIS M. RINEHART
Deputy Chief of Staff for
Information Management

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